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.

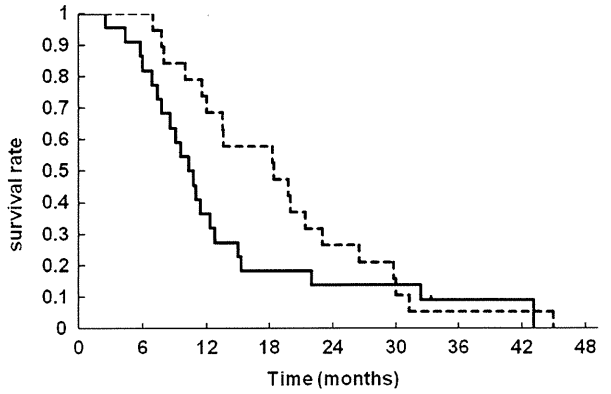

Fig. 1 Kaplan–Meier survival curves for recurrent MG cases treated by BNCT. The continuous line shows the survival of all patients after BNCT ($n = 22$). The broken line shows the survival of GBM (on-study histology) after diagnosis of GBM ($n = 19$)

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

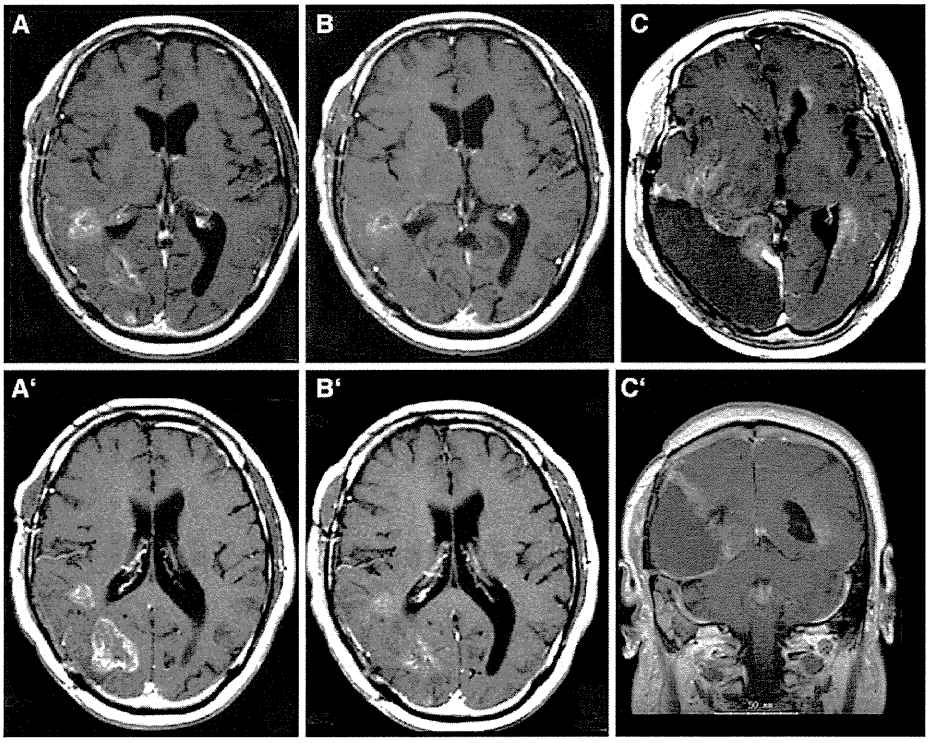

Fig. 2 A representative case of recurrent GBM treated by BNCT. (**a**, **a**′) MRI, prior to BNCT. Gd-enhanced lesions were at the right temporo-occipital lobe; (**b**, **b**′) MRI, 48 h after BNCT. Marked shrinkage of the lesions was recognized; (**c**, **c**′) MRI, 7 months after BNCT. CSF dissemination 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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定位的放射線治療
13：23～30, 2009

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要旨：ホウ素中性子捕捉療法（BNCT）は，理論上腫瘍細胞に選択的照射の可能な粒子線治療である。我々は2002年1月以降，熱外中性子および集積機序の異なる2種類のホウ素化合物（BSH, BPA）を併用した改良型BNCTを用い，50例以上の悪性神経膠腫を治療してきた。改良型BNCTは非開頭で行い，個々の患者でホウ素化合物の腫瘍内集積を考慮し線量計画を行っている。最近では，BPAを700 mg/kgまで増量し，6時間で点滴することで腫瘍内のホウ素濃度を均一化し，照射線量を高めるとともに，新規診断例に対してはX線分割外照射を併用している。新規診断神経膠芽腫で，平均生存期間は診断後23ヵ月（n＝11）であった。選択的照射であるBNCTに外照射を加えることで，新規診断例の治療成績は向上した。また，再発症例においても，他の臨床研究より好成績を示し，予後不良とされるサブグループにおいて有効性が高い傾向が見られた。

Key words：アルファ粒子，ホウ素中性子捕捉療法，悪性神経膠腫

はじめに

悪性神経膠腫はきわめて予後不良の原発性脳腫瘍であり，治療に難渋する最も大きな原因は，腫瘍の浸潤性性格にある。腫瘍の辺縁は明瞭ではなく，細胞レベルでは画像上の造影域を越え，最低でも周囲の正常脳2 cmまでは腫瘍細胞が存在するとされる。そのため，腫瘍の造影域を手術により全摘出しても，再発が必至であり，摘出手術および術後のX線分割外照射・テモゾロミドによる化学療法が，現在の標準的治療法であるが，新規診断例における生存期間中央値は約14ヶ月である[1]。

我々は，前述の浸潤部腫瘍細胞をも選択的に標的可能となる，ホウ素中性子捕捉療法（Boron Neutron Capture Therapy；BNCT, Fig. 1）[2]に注目し，2002年1月以降，52例の悪性脳神経膠腫を治療してきた。我々のBNCTは，熱外中性子を用いた非開頭照射で行い，集積機序の異なる2種類のホウ素化合物（BSH, BPA）を併用したもので，これまでの欧米・本邦での治療プロトコールとは全く異なる改良型である[3-8]。

今回我々は，当施設にて治療を行った，新規

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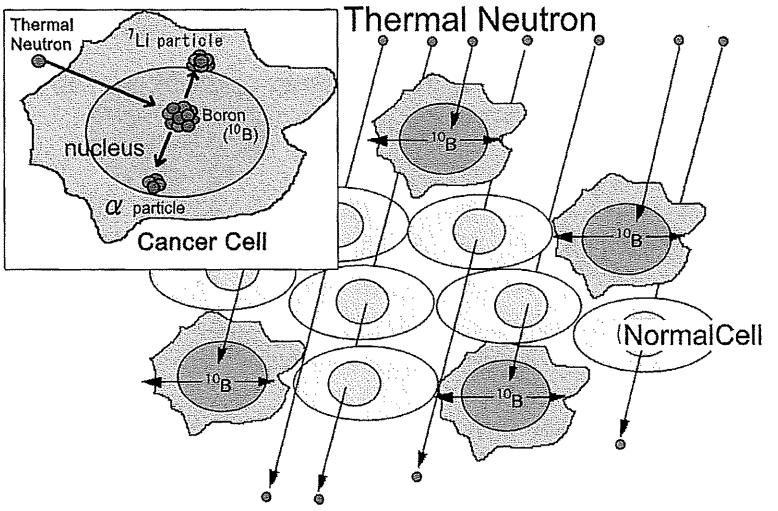
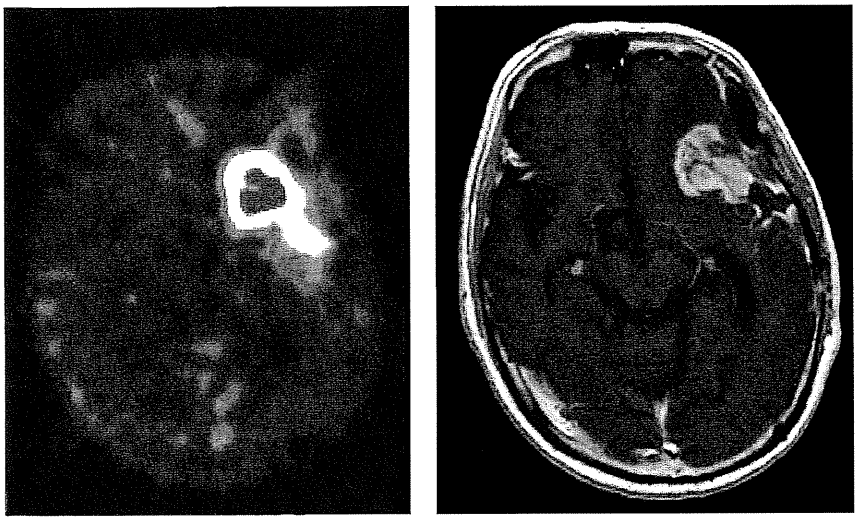


Figure 1 The principle of boron neutron capture therapy (BNCT).
BNCT is a binary approach: A boron-10 (10 B)-labeled compound is administered that delivers high concentrations of 10 B to the target tumor relative to surrounding normal tissues. This is followed by irradiation with thermal neutrons or epithermal neutrons that become thermalized at depth in tissues. The short range (5–9 micrometer) high energy of the alpha and 7 Li particles released from the 10 B (n, alpha) 7 Li neutron capture reaction make tumor selective killing without damage for adjacent normal brain tissue.

診断および再発性の悪性神経膠腫に対する改良型 BNCT の治療成績について解析を加え報告する。

I. 対象と方法

2002 年 1 月から 2007 年 12 月までに，大阪医科大学・脳神経外科で治療を行った悪性神経膠腫は，52 例であった。BNCT は，2 種類のホウ素化合物（BSH および BPA）の併用，熱外中性子による非開頭照射で行い[4]，照射前の^{18}F-BPA PET によるホウ素化合物 BPA の集積 (Fig. 2)[9]および血中ホウ素濃度から，個々の患者の線量計画を行った[3,6,8]。中性子源としては，主として京都大学原子炉実験所（大阪府・熊取）KURRI を利用し，メンテナンスなどの事由で使用不可の期間に関しては日本原子力開発研究機構（茨城県・東海）JRR-4 を利用して行った。本報告では，これらから，元疾患以外の死因によるもの，追跡期間が短期間の生存例，死因が不明または追跡不能例などを除外し解析を行った。新規診断の膠芽腫（WHO grade IV）は 21 例で，これまでに当施設で標準治療（放射線・化学療法）により治療を行った 27 例と比較検討を行った。初発膠芽腫の治療例 21 例中，最近の 11 例では，BNCT 後に 20～30 Gy の X 線分割外照射を加えた。照射線量は，BNCT 時に照射された正常脳の最大線量から算出し，必要に応じて減量した。また，再発悪性神経膠腫では，22 例（膠芽腫 19 例）に BNCT を行い，生存期間に関し解析した。さらに予後因子別のサブ解析として，新規診断例では RTOG（手術，放射線治療）[10]および EORTC（手術，テモゾロミド併用放射線治療）[11]の RPA class 解析の結果と，また再発例に対しては NABTT の RPA class 解析の結果[12]と比較検討を行った。生存解析には Kaplan-Meier 法を用い，Log-rank test にて検定を行った。また Cox 比例ハザードモデルにおける解析を用い，ハザード比を解析した。BNCT 施行後，全例で定期的な MRI 画像による評価を行い，再発または放射線壊死の診断には^{18}F-BPA PET を用い，診断に応じて治療を行った[13]。



^{18}F BPA PET　　MRI（T 1 Gd）
（T/N : Tumor/Normal Brain ratio）＝7.8

Figure 2 ^{18}F labeled BPA positron emmision tomography（F-BPA PET）
F-BPA PET has been applied for the estimation of the boron compound accumulation prior to BNCT. The tracer is fluororide labelled boron compound. This PET ensures the effectiveness of BNCT. F-BPA accumulates well and distributes precisely in the tumor lesion and the infiltrating tumor zone.

II. 結果

A. 画像所見および合併症・死因

全例で，BNCT による急性・亜急性の重篤な合併症は経験しなかった。初期の症例で，ホウ素化合物の再結晶化による腎毒性が観察されたが，その後の症例では十分な補液，利尿を行い容易に克服できた。

初発，再発を問わず，全例で画像上の腫瘍の縮小を認め，画像上 50% を超える造影域の縮小は 67% の症例に認めた[5]。また，BNCT 施行後に，ステロイド剤や高浸透圧利尿剤を用いることなく造影域周囲の浮腫は軽減した。死因としては初発，再発ともに髄腔内播種が高率であり，初発例では放射線壊死が死因となった例はなかったが，再発腫瘍に対する BNCT 後には 22 例中 3 例で放射線壊死が生じた。

B. 生存解析

1. 新規診断膠芽腫に対する BNCT（Fig. 3）

組織診断確定時からの生存期間中央値（MST）は，BNCT 群 21 例で 15.6（95% CI ; 12.2–23.9）ヶ月であり，施設コントロール群（手術，放射線，化学療法）27 例の 10.3（7.4–13.2）ヶ月を有意に上回った（Fig. 4, Log-rank test, p＝0.0035）。このコントロールを比較対象としたハザードモデルでは，ハザード比 0.399（p＝0.0038）であった。また，BNCT に外照射を加えた群 11 例では，MST が 23.5（10.2－）ヶ月と有意に延長し，コントロールに対するハザード比は 0.323（p＝0.004）となった（Fig. 5）。

RTOG RPA class 分類では，class III が 6 例，VI が 6 例，V が 8 例，VI は 1 例であり，それぞれ MST は，23.5, 16.9, 13.2, 9.8 ヶ月であった。これは RTOG（手術，放射線治療）での MST（III ; 17.9, IV ; 11.1, V ; 8.9, VI ; 4.6）[10] および EORTC（手術，テモゾロミド併用放射線治療）での MST（III ; 21.4, IV ; 16.3, V ; 10.3）[11] を上回る結果であった（Fig. 6）。

2. 再発悪性神経膠腫に対する BNCT

BNCT からの MST は，全 22 例で 10.8（7.3

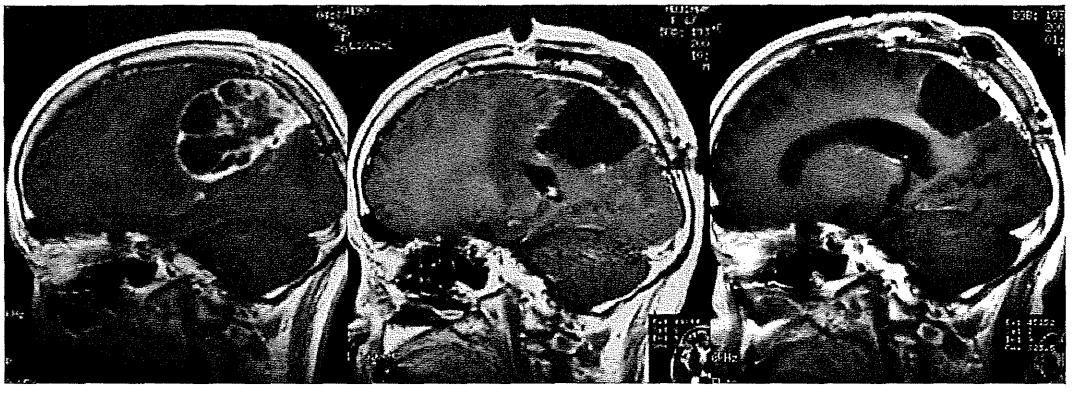


Figure 3 63 y.o., F., Newly diagnoised glioblastoma patient.
She was treated by surgical removal and BNCT followed by external beam X-ray irradiation (2 Gy/day, total 30 Gy). The deepest part of the tumor was 7.5 cm from the scalp in this case. The irradiated minimum tumor dose by BNCT was improved by the air-instilation methods from 18.9 (without air) to 26.9 (with air) Gy-Eq. (left : prior to surgical removal, middle : after surgery, prior to BNCT, right : 44 months after treatment)

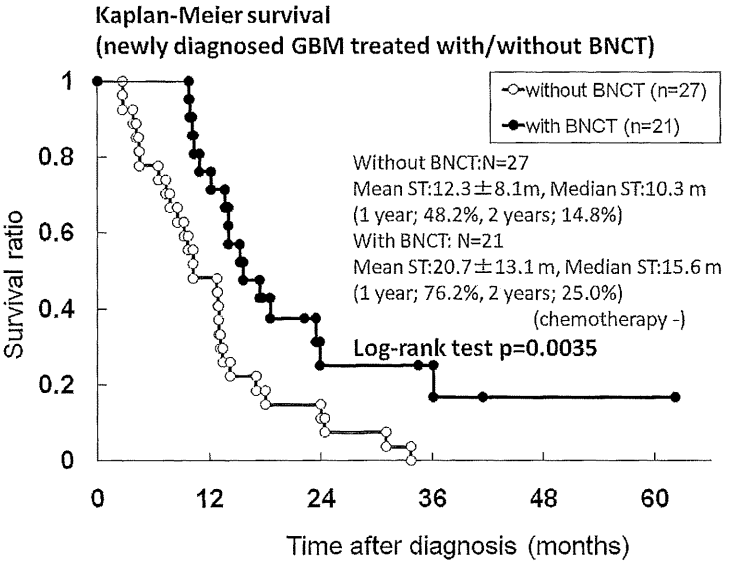


Figure 4 Cumulative data for all newly diagnosed glioblastoma (WHO grade 4, n=21).
This is our recent historical control (gray line) in our institute treated mainly by nitrosourea plus irradiation. The median survival time of BNCT group (black line) is 15.6 months without chemotherapy until tumor progression. There is statistical significance between both group in Log-rank test (p=0.0035).

–12.8) ヶ月であり，再発時の組織診断が膠芽腫であった19例では，9.6 (6.9–11.4) ヶ月であった。これは，NABTT の報告に含まれた全再発悪性神経膠腫の MST (7.0 ヶ月，n=310) より良好な結果であった。また，膠芽腫 19 例の，再発と診断されてからの MST は 19.1 (11.6–23.0) ヶ月であった (Fig. 7)。

NABTT による再発神経膠腫の RPA class 分類において，最も予後不良とされる class 3 が 3 例 (14%)，class 7 は 7 例 (32%) 含まれ，

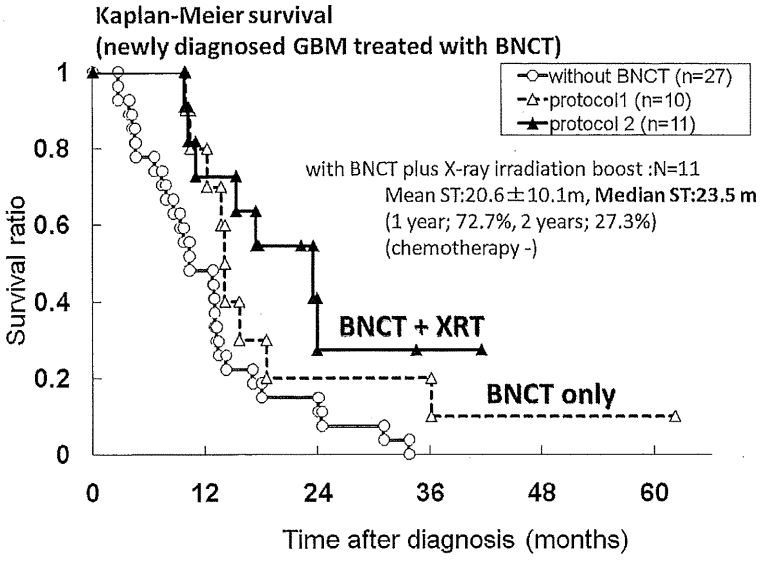


Figure 5 Cumulative data for all newly diagnosed glioblastoma (protocol 1 and 2).
External beam X-ray irradiation (XRT) boost after BNCT (protocol 2, black the median survival time as 23.5 months (vs 14.1 months for BNCT only (protocol 1, dotted line and open triangle)).

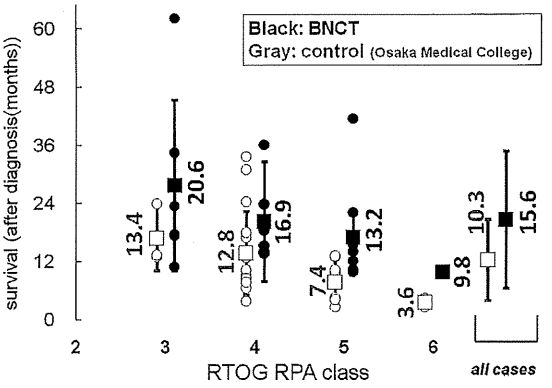


Figure 6 Survival of the corresponding RPA subclasses by RTOG (Curren, 1993).
Mean (square) and individual (circle) survival (bars showing standard deviation) of all cases and each RTOG RPA classes.

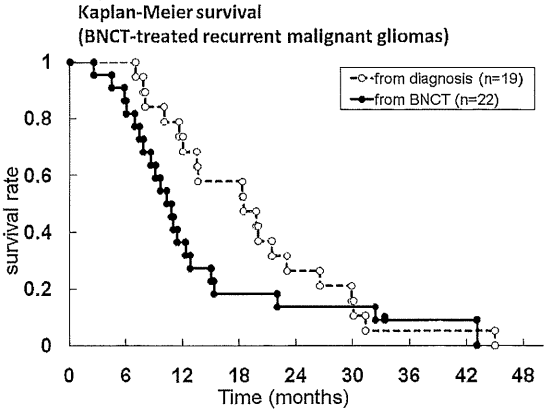


Figure 7 Figure Kaplan-Meier survival curves for the recurrent malignant glioma cases (WHO grade 3&4) treated by BNCT.
A continuous line shows the survival of all patients after BNCT (n=22). A dotted line shows the survival of GBM (on-study histology) after diagnosis of GBM (n=19).

それぞれ BNCT による MST が 11 ヶ月，11 ヶ月と，報告による 3.8, 4.9 ヶ月を大きく上回り（class 3＋7；4.4（3.6–5.4）ヶ月 vs 9.1（4.4–11.0）ヶ月），その他の class においても概ね良好な結果が得られていた。

III. 考察

悪性神経膠腫は，浸潤性の原発性悪性腫瘍であり，手術単独での治癒は望めない。術後の放射線治療は有意に予後を延長させ，近年ではこれにテモゾロミドによる化学療法を加えた治療が標準的に行われているが，その生存期間は約14ヶ月であり，本腫瘍を克服したとは言い難い[1]。

放射線を用いた新しい展望として，ガンマナイフやリニアックによる定位的放射線照射，陽子線，重粒子線および中性子捕捉療法などが現在期待されている。定位的照射に代表される局所高線量照射は，あくまで手術摘出困難な部位における残存腫瘍塊に対して，手術の補助的役割を担う治療法であり，いかに正確にかつ均一に線量を局所に集中させたとしても，浸潤性性格の強い悪性神経膠腫に対して治癒は望めない。これらの線量計画は，画像診断をもとに治療医が行うもので，開頭手術における術者が摘出範囲を決定するのと同様，辺縁部からの再発は免れない。治療範囲の拡大は，外科治療と同様，治療による合併症を高率に招くことになる。放射線治療の中で中性子捕捉療法は，局所高線量という性格を有しながら，腫瘍を細胞レベルで標的とし，正常脳に浸潤した腫瘍細胞をも選択的に治療できるという“細胞選択的粒子線治療”であり，他の放射線治療とは異なる概念を有する画期的な治療法として注目される[2]。

BNCTにより治療を行った，新規診断膠芽腫症例における全生存期間の解析では，中央値が有意差をもって延長し，旧来の標準治療（手術，放射線・化学療法（主としてACNU））の成績より効果があることが示された。今回のBNCT治療群では，初期治療としての化学療法は一切行っておらず，今後BNCTにテモゾロミドを併用することでこの成績はさらに改善しうると考える。さらにハザードモデルでは，コントロール群に対するハザード比は0.4未満で，この数値はランダム化比較検討試験を組む際に，一群あたり20～30症例で有意な差をもって治療効果を示しうる値である。これらの治療群は，何らかのバイアスが存在しうるが，RTOGのRPA class分類による予後因子別の解析を見ても，BNCT治療群は優れた治療成績を示していた。またEORTCによる放射線・テモゾロミドの治療群との比較においても，わずかではあるがすべてのclassでBNCT群が上回っていた。EORTCの報告では，テモゾロミドによる生存期間の延長は，予後良好群ほど大きかったとされるが，我々のBNCTによる治療効果は，予後不良とされるものほど効果が大きい傾向を示した。

悪性神経膠腫では，現時点での初発例に対する治療方針は，前述のごとくであるが[1]，再発例に対する治療方針は，有効とされる標準的なものは一切無く，再発からの生存期間は約6ヶ月である[14,15]。今回我々が示した再発悪性神経膠腫に対する治療成績は，約11ヶ月と良好であるが，比較対象となる治療群は存在せず，この数値のみをもって有効とするには無理がある。そこでこのBNCTによる治療成績を，再発悪性神経膠腫の臨床試験（NABTTの10個のphase I, IIに登録された333例の解析）から得られた予後因子による分類と比較した。これによると，最も予後不良とされたclass 3＋7でのMST 4.4（3.6–5.4）ヶ月に対し，BNCT治療群は9.1（4.4–11.0）ヶ月と大きく上回っていた。

我々の改良型BNCTによる治療では，特に予後不良とされるグループにおいて，治療効果が高かった。悪性神経膠腫のごとく浸潤性に発育する腫瘍では，周囲組織への影響が懸念されるが，BNCTは，細胞選択的粒子線治療という特徴から，正常細胞への影響が少なく高線量による放射線治療が可能となるためと考える。

IV. 結語

我々の改良型BNCTは，悪性神経膠腫の新規診断例および再発例に対し，安全に施行しうる有効な治療手段であり，生命予後を改善した。選択的照射であるBNCTにX線外照射を加えることで，新規診断例の治療成績は向上した。また特に，予後不良とされるサブグループ，治療困難例において，有効性が高い傾向が見られた。

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Therapy effects of boron neutron capture therapy for malignat glioma

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Boron neutron capture therapy (BNCT) is cell selective particle irradiation based upon the nuclear reaction that occur when non-radioactive boron-10 (^{10}B) is irradiated with low energy neutrons to produce high energy alpha particles.

Since 2002, we have treated >50 cases of malignant gliomas with our modified BNCT utilizing sodium borocaptate (BSH) and boronophenylalanine (BPA) simultaneously. Modified BNCT was carried out without craniotomy using epithermal neutron beam. We used ^{18}F-BPA-PET for almost all the patients who will receive BNCT to estimate the irradiation dose. Recently, we increased the amount of BPA and prolonged the infusion time (700 mg/kg, 6 hours) to give a more homogeneous distribution of boron compounds, even in the infiltrating lesion. Farther more, for the newly diagnosed case, patients were treated with BNCT followed by fractionated X-ray irradiation (XRT) of 20 to 30 Gy.

The median survival time (MST) of newly diagnosed glioblastoma was 21 months (n=11). With BNCT followed by XRT boost, the MST was significantly extended. Also for the recurrent malignant glioma cases, we showed the survival benefit compare with other clinical studies.

Our modified BNCT protocol showed favorable results of patients with malignant glioma not only for those with good prognoses but also for those with poor prognoses.

Key words : alpha particle, boron neutron capture therapy, malignant glioma

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Boron neutron capture therapy

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 was delivered as the mean dose 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 constructed at our institute was confirmed from a clinical viewpoint in BNCT for multiple liver tumors and MPM.
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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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Material and methods

Accelerator

Our AB-BNCT system consists of a cyclotron accelerator that produces a proton beam of ~2 mA at 30 MeV, beam transport system, beam scanning system on the beryllium target, target cooling system, neutron-beam-shaping assembly (BSA), multileaf collimator, and an irradiation bed for patients in both sitting and decubitus positions. Fig. 1 shows a schematic layout of the BSA for production of epi-thermal neutrons.

The Li(p,n) reaction at low proton energy is widely accepted as the most promising for epi-thermal neutron generation [9]. However, we selected the Be(p,n) reaction with 30 MeV for our AB-BNCT system because: (1) the system using Li(p,n) reaction needs an accelerator with a current of >5 mA to yield an intensity of epi-thermal neutron flux of 1×10^9 n/cm^2/s. No accelerator is presently available to achieve such a high current; (2) it is difficult to stably operate a lithium target with heat >10 kW because the 180 °C melting point of lithium is much lower than that of beryllium, which is 1278 °C; and (3) the Be(p,n) reaction with 30 MeV has a higher neutron yield compared with the Li(p,n) reaction. The neutron yield of the Li(p,n) reaction with 1.9 MeV (near threshold) is about 2.4×10^{-6} (neutrons/proton) [9]. Whereas, the neutron yield of the Be(p,n) reaction with 30 MeV is about 3.0×10^{-2} (neutrons/proton) [10].

The reaction of a proton with the beryllium target emits high energy neutrons at up to 28 MeV in the 0° direction. The 0° neutron yield is the largest. The BSA consists of lead, iron, calcium fluoride, and aluminum for reducing neutron energy and shaping an epi-thermal neutron beam. The BSA is surrounded by polyethylene material for shielding fast neutrons and for decreasing radiation to the patient's body. The γ-ray dose contamination in the treatment neutron beam increases because of γ-rays coming from the neutron capture in hydrogen materials such as polyethylene. However, the γ-ray dose contamination per epi-thermal neutron in a treatment beam under free-air conditions is 7.75×10^{-14} Gy cm^2 (epi-thermal region is from 0.5 eV to 40 keV). This value is sufficiently below than the IAEA-TECDOC-1223 target value of 2×10^{-13} [11].

KUR

KUR is a light water-moderated, tank-type nuclear research reactor, with a nominal power of 5 MW. The Heavy Water Neutron Irradiation Facility (HWNIF) is a bio-medical facility at KURRI. The facility has been previously described in detail [12,13]. The higher energy neutrons are moderated by the epi-thermal neutron moderator, which is the mixture of aluminum and heavy water (80%/20% in volume). The heavy-water spectrum shifter is installed outside of the epi-thermal neutron moderator, for control of the neutron-energy spectrum. The total heavy-water thickness can be changed from 0 to 90 cm in 10-cm increments. The thermal neutron filters of cadmium and boral are installed outside of the spectrum shifter, to regulate the thermal neutron component. The apertures of these filters are changed from 0 to 62 cm. Outside of the filters, the bismuth layer is placed for γ-ray elimination. In this facility, neutron beams with various energy spectra from almost pure thermal to epi-thermal are available by controlling the heavy-water thickness in the spectrum shifter, and by the opening and closing of the cadmium and boral thermal neutron filters.

Comparison of neutron spectra

A comparison has been carried out between the neutron spectra at the output port in air for AB-BNCT and RB-BNCT. For the KUR, the neutron spectrum was measured by activation of gold foils. For the accelerator-based neutron source, the neutron spectrum was obtained by simulations from a calculated neutron source.

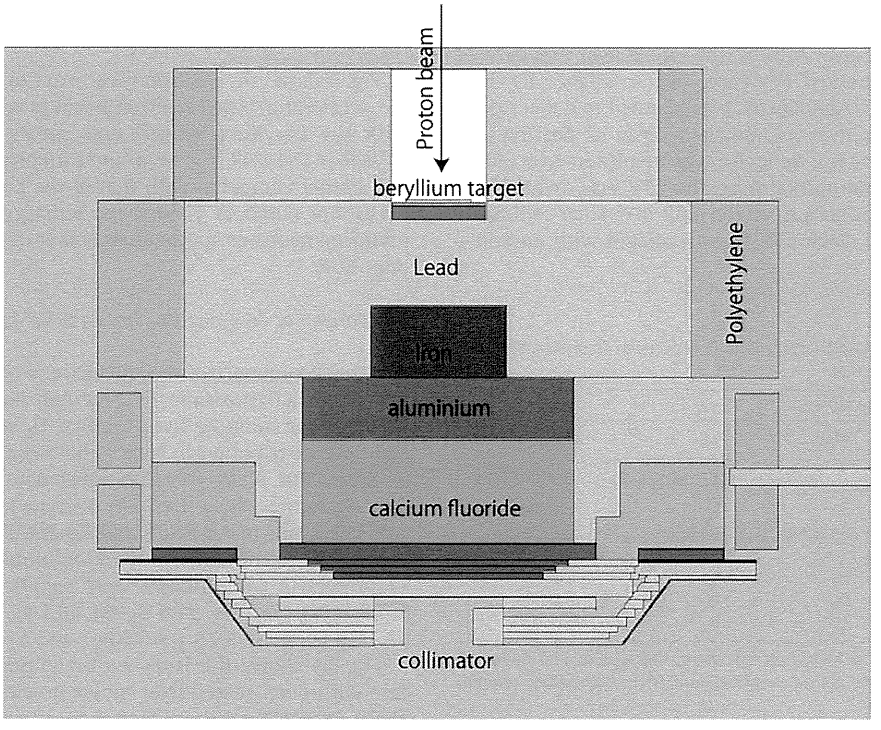

Fig. 1. Schematic layout of BSA for production of epi-thermal neutrons based on beryllium (p,n) reaction using 30 MeV proton beam.

Assumption and parameters for BNCT treatment planning

The conditions and parameters in BNCT treatment planning are summarized in Table 1. The parameters were approximately the same as those in our previous treatment planning studies on BNCT for multiple liver tumors and MPM [5,6]. The details for determination of each parameter have been described in our previous reports [5,6]. The compound biologic effectiveness (CBE) factors of the boron compounds in Table 1 were requested to convert the physical dose of BNCT to the photon-equivalent dose (Gy-Eq) and the relative biologic effectiveness (RBE) of each component of the beam. The CBE factors were used as an alternative RBE in evaluating the biologically equivalent absorbed dose by BNCT. This was because the same or different boron compounds might yield variable effects on different tissues, as a result of variations in the microdistribution of the boron compounds and the morphological character of the target cells. The CBE factors and RBE values for the tumors were the same as those used in clinical BNCT trials [14,15]. The CBE factors and RBE values for liver and lung were determined by experimental studies using rodents [16,17]. We adopted the value of 3.0 as the RBE value of $^{14}N(n,p)^{14}C$ radiations and fast neutrons for liver. The value was greater than the RBE of fast neutron for hepatocytes reported by Ono et al. [18]. Use of the greater RBE for normal liver is expected to decrease the occurrence of radiation-induced liver disease in clinical situation.

The difference in the method between BNCT for multiple liver tumors and MPM was the drug delivery system (DDS) for the boron compounds. In BNCT for multiple liver tumors, borocaptate sodium (BSH), which has been employed as a boron compound in clinical BNCT trials for malignant glioma, was administered via the hepatic artery with vessel occlusion materials (lipiodol), according to our previous reports [3,5,7]. This DDS method is possible to deliver ^{10}B to liver tumors, that are highly selective [3]. In the present study, ^{10}B tumor/liver concentration ratio was assumed to be 20 according to our present study (Table 1) [3]. In BNCT for MPM, boronophenylalanine (BPA), another boron compound available in clinical trials, was administered intravenously [8]. In the MPM cases, ^{10}B tumor/lung or liver concentration ratio was assumed to be 3.5 (Table 1).

In BNCT for multiple liver tumors, the whole liver was defined as the clinical target volume (CTV). Three-port irradiation by anterior, right and posterior (ARP) beams was planned to deliver thermal neutrons to whole liver as homogeneously as possible [5]. Because the CTV for MPM was defined as the hemithorax, including the tumor and ipsilateral normal lung, the CTV was divided into upper and lower portions because of the limit in circular collimator size (maximum 25 cm). Each CTV was irradiated with anterior–posterior (AP) beams or 20–30° anterior-oblique and posterior-oblique beams. The oblique beams were used to deliver greater doses to the tumors at mediastinal side compared to AP beams in some cases. Four-port irradiation was needed for covering the whole CTV.

Table 1
^{10}B concentrations and RBE and CBE factors used for conversion of physical dose (Gy) to photon-equivalent dose (Gy-Eq).

	Liver tumor	MPM	Liver	Lung
^{10}B concentration (ppm)	200.0	84.0	10.0 (Liver tumor cases) 24.0 (MPM cases)	24.0
RBE, CBE				
$^{10}B(n,a)^{7}Li$	2.5 ($CBE_{for\ BSH}$)	3.8 ($CBE_{for\ BPA}$)	0.94 ($CBE_{for\ BSH}$)* 4.25 ($CBE_{for\ BPA}$)*	2.3 ($CBE_{for\ BPA}$)†
$^{14}N(n,p)^{14}C$	3.0	3.0	3.0	2.2†
Fast neutron	3.0	3.0	3.0	2.2†
γ-Ray	1.0	1.0	1.0	1.0

Abbreviations: RBE = relative biological effectiveness; CBE = compound biological effectiveness; MPM = malignant pleural mesothelioma; BSH = borocaptate sodium; BPA = boronophenylalanine.
* Data from Suzuki et al. [16].
† Data from Kiger et al. [17].

Overview of BNCT treatment planning using the simulation environment for radiotherapy applications (SERA) system

Computed tomography (CT) images of four patients with multiple liver tumors and six with MPM were used in the present study. Three patients had right MPM, and the other three had left MPM. In four BNCT treatment plans for multiple liver tumors, a total of 11 liver tumors were evaluated.

We have already reported the treatment planning studies on BNCT for multiple liver tumors and MPM using KUR epi-thermal neutron beam data and the SERA system, a currently available BNCT treatment planning system. Details of the procedures in treatment planning using the SERA system have been described in our previous reports [5,6].

Dose–volume histogram (DVH) analysis

The SERA system can provide DVH data for each tumor or for the normal tissues as a whole. The maximum, minimum and mean doses to the tumors and normal tissues were assessed for each case. In radiotherapy for liver tumors and MPM, radiation-induced liver injury and radiation pneumonitis are dose-limiting toxicities, therefore, we set the doses delivered to normal liver and lung tissues as constraint doses. In the present study, 5.0 Gy-Eq of the mean liver and lung doses were set as the constraint doses. Under these conditions, each DVH parameter and irradiation time was compared between AB-BNCT and RB-BNCT. The doses delivered to the tumors with AB-BNCT and RB-BNCT were compared by means of Wilcoxon's signed-rank test.

Results

Neutron spectra comparison

Fig. 2 shows the neutron spectra at the output port produced by the accelerator-based neutron beam (1 mA, 30 MeV proton beam with the beryllium target) and epi-thermal neutron beam of HWNIF in the KUR. The neutron beam produced by the accelerator was harder compared with that of the KUR. In comparison of the maximum numbers yielded per lethargy, the accelerator source produced neutrons approximately four orders of magnitude higher than KUR.

Comparison of dose distributions in BNCT for multiple liver tumors

Table 2 summarizes the DVH parameters for tumor and normal liver and irradiation time for three-port irradiation in AB-BNCT and RB-BNCT for multiple liver tumors. To compare irradiation time and dose distribution in tumors between AB-BNCT and RB-BNCT, all treatment plans were normalized to deliver mean doses of 5 Gy-Eq to the whole liver. The average irradiation time was 43.8 and 198.3 min in AB-BNCT and RB-BNCT, respectively. The averages of the maximum, mean and minimum doses delivered to all 11 tumors in the AB-BNCT were significantly higher than those in RB-BNCT (78.7 vs. 77.4 Gy-Eq, 68.1 vs. 65.1 Gy-Eq and 57.7 vs. 53.7 Gy-Eq, $p = 0.0023$, $p = 0.0040$, and $p = 0.0022$, respectively).

Fig. 3A shows the isodose distributions in the representative case with deep-seated liver tumor provided by RB-BNCT and AB-BNCT. AB-BNCT delivered higher dose to the tumor than RB-BNCT. Fig. 3B shows the depth–dose distribution profiles along the right

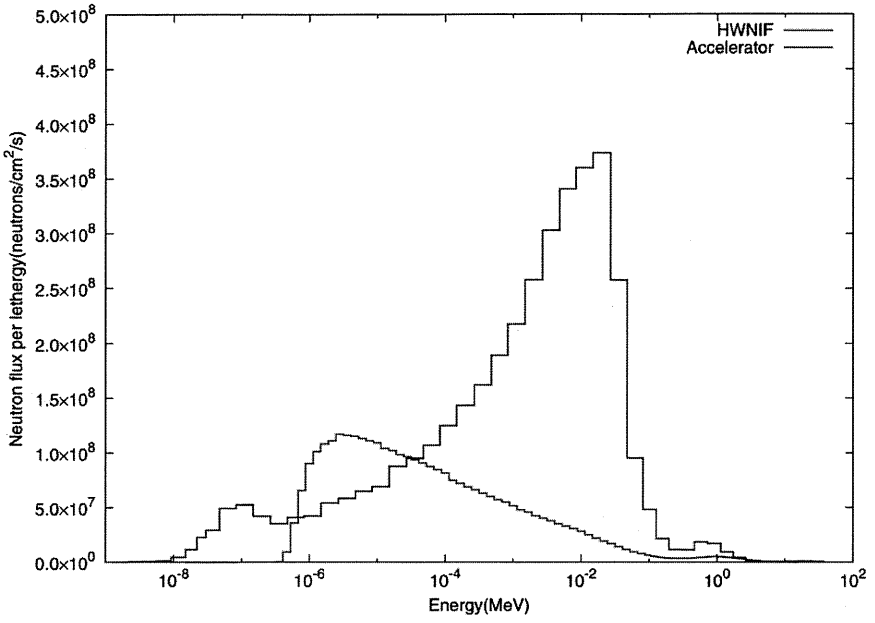

Fig. 2. Comparison of neutron spectrum between HWNIF and accelerator-based neutron source shaped with the BSA.

neutron beam axis which passed into the deep-seated liver tumor. The depth–dose profiles in the tumor located at a depth of 9.0–12.5 cm demonstrated that AB-BNCT delivered a higher dose than RB-BNCT. Fig. 3C shows the depth-ratio of thermal neutron fluence-rate (AB-BCNT to RB-BNCT) profiles along the same beam axis as in Fig. 3B. The ratio of thermal neutron fluence-rate increased from 3.9 to 6.3 at a depth of 1–12 cm, which was caused by the property of the accelerator-based neutron source which has a peak at higher energy in its neutron spectrum compared with that of the KUR as shown in Fig. 2.

Comparison of treatment parameters in BNCT for MPM

Table 3 compares the DVH parameters for tumor and normal lung and irradiation time for four-port irradiation in AB-BNCT and RB-BNCT for MPM. To compare irradiation time and dose distribution in the tumor between AB-BNCT and RB-BNCT, all treatment plans were normalized to deliver mean doses of 5 Gy-Eq to the whole of the ipsilateral lung. The average irradiation time in AB-BNCT and RB-BNCT were 29.9 and 134.7 min, respectively. The mean doses delivered to the MPM tumors by AB-BNCT and RBNCT were 20.2 and 19.9 Gy-Eq, respectively. The average of the maximum doses delivered to the MPM tumors by AB-BNCT was significantly lower than those with RB-BNCT (36.4 vs. 40.0 Gy-Eq, $p = 0.0253$). On the other hand, the average of the minimum doses delivered to the MPM tumors by AB-BNCT was significantly higher than those with RB-BNCT (4.6 vs. 4.3 Gy-Eq, $p = 0.0275$).

Fig. 4A shows the isodose distributions for the tumor in the representative case with MPM provided by RB-BNCT and AB-BNCT. AB-BNCT delivered higher dose to the MPM tumor located in the middle of the thorax compared to RB-BNCT. Fig. 4B shows the depth–dose distribution profiles along the anterior epi-thermal neutron beam axis in the case of MPM. The tumor located at a depth of 9.0–12.5 cm received a greater dose with AB-BNCT compared with RB-BNCT. On the other hand, RB-BNCT delivered a greater dose to the tumor located at a depth of 3.5–5.0 cm. Fig. 4C shows the depth–thermal neutron flux ratio (AB-BCNT to RB-BNCT) profiles along the same beam axis as Fig. 4B. The thermal neutron flux ratio increased from 4.0 to 5.8 within a depth of 1–12 cm.

Discussion

In BNCT for multiple liver tumors and MPM, the most important feature of the AB-BNCT system at our institute is capability to deliver three- or four-port irradiation within a reasonable treatment time (<1 h), including the time required for changing patient position. Shortening of irradiation time makes it possible to finish irradiation while maintaining a high ^{10}B concentration in the tumor, and to reduce the non-selective background dose. In addition, shortening of irradiation time provides comfort to the patients during irradiation and single or two-fractionated BNCT has economic benefits.

Another important feature of the AB-BNCT system is its capability of delivering greater doses to deep-seated tumors than RB-

Table 2
Irradiation time and DVH parameters showing averages (with range) for liver tumors and normal liver.

Neutron source	Irradiation time (min)	Tumor			Liver		
		D_{max} (Gy-eq)	D_{mean} (Gy-eq)	D_{min} (Gy-eq)	D_{max} (Gy-eq)	D_{mean} (Gy-eq)	D_{min} (Gy-eq)
KUR	198.3 (177.0–216.8)	77.4 (49.3–104.6)	65.1 (33.8–84.2)	53.7 (20.7–76.5)	6.9 (6.4–7.4)	5.0*	1.9 (1.3–2.1)
Accelerator	43.8 (39.0–47.8)	78.7 (52.6–102.0	68.1 (37.7–87.1)	57.7 (23.6–76.7)	6.7 (6.3–7.2)	5.0*	1.7 (1.1–2.2)

Abbreviations: DVH = dose-volume histogram; KUR = Kyoto University Research Reactor.
* The mean dose to the liver normalized to 5.0 Gy-Eq.