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Long-survivors of glioblatoma treated with boron neutron capture therapy (BNCT)

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ABSTRACT

The purpose of this study was to compare the radiation dose between long-survivors and non-long-survivors in patients with glioblatoma (GBM) treated with boron neutron capture therapy (BNCT). Among 23 GBM patients treated with BNCT, there were five patients who survived more than three years after diagnosis. The physical and weighted dose of the minimum gross tumor volume (GTV) of long-survivors was much higher than that of non-long survivors with significant statistical differences.

1. Introduction

Since 1998, we have performed BSH-based intra-operative BNCT (IO-BNCT). The clinical outcomes of IO-BNCT were favorable in patients whose GBMs were located within a 4 cm depth from brain surface. However, they were unsatisfactory in patients whose tumor was situated in deeper regions, because neutron fluence delivery into the deep regions was inadequate (Hatanaka and Nakagawa, 1994; Nakagawa and Hatanaka, 1997; Nakagawa et al., 2003). To improve the neutron beam delivery epithermal neutron beam was developed. Moreover, computational dosimetry system based on CT and MRI scan was developed. The introduction of epithermal neutron beam and new modality of dose planning system could make it possible for clinical application of non-operative BNCT (NO-BNCT) using the combination of BSH and BPA. We have shifted from IO-BNCT to NO-BNCT since 2005. We have already reported the clinical results of BNCT using mixed epithermal neutron beams in patients with malignant glioma treated with IO-BNCT (Kageji et al., 2006). In this study, a statistically significant correlation between the gross tumor volume (GTV) dose and median survival time was found. The median survival time was 19.5 months and one- and two-year survival rate was 60.6% and 37.9%, respectively.

2. Material and method

We have treated 23 newly-diagnosed GBM patients with BNCT, including 17 patients with IO-BNCT, in which 100 mg/kg of BSH were given, and seven patients with NO-BNCT, in which 250 mg/kg of BPA and 100 mg/kg of BSH were given to patient intravenously. BNCT radiation dose was evaluated with physical boron (Gy) dose and weighted dose (Gy(w)) using JAERI Computational Dosimetry System (JCDS). We analyzed BNCT dose in gross tumor volume (GTV) and clinical target volume (CTV). The GTV was concomitant with enhancement area on Gd-MRI. The CTV was concomitant with high intensity area on T2-weighted MRI. We compared radiation doses between those who survived more than three years (long-survivor group) and those who survived below three years (non-long-survivor group) after diagnosis. The value of weighted factors to tumor of BSH and BPA were 2.5 and 3.6, respectively (Figs. 1 and 2).

3. Results

Among 23 GBM patients, five patients have survived more than three years after diagnosis (5/24 patients; 21%), including four patients in IO-BNCT, one patient in NO-BNCT. Nineteen patients died within three years after BNCT, including 13 patients in IO-BNCT, six patients in NO-BNCT. Mean value of survival time in long-survivor group was 1861 ± 485 days (range from 1558 to 2710 days). Three patients died of wound infection, myocardial infarction and pneumonia. Two patients are still alive. These five patients were suffered from no tumor recurrence.

Long- and non-long-survivor groups in minimal GTV physical dose were 21.2 ± 8.3 and 14.2 ± 5.3 Gy ($p=0.03$), respectively. These in minimal GTV weighted dose were 59.7 ± 22.6 and 43.1 ± 12.9 Gy(w) ($p=0.04$), respectively (Table 1). According to the CTV dose, these in minimal physical dose were 13.1 ± 9.9 and 8.7 ± 4.1 Gy ($p=0.14$), respectively, and in minimal weighted dose were 38.9 ± 27.0 and 28.1 ± 11.1 Gy(w) ($p=0.18$), respectively (Table 2). All long-survivors suffered from severe radiation

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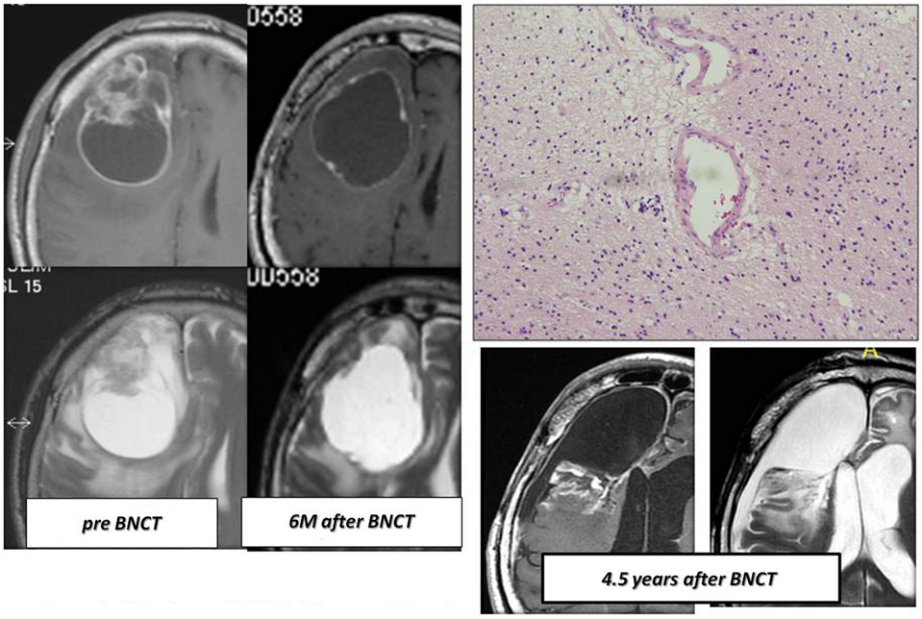

Fig. 1. Case 1: right frontal GBM 48-year-old male. Left: Gd- and T2-MRI before BNCT, middle: Gd- and T2-MRI six months after BNCT. Right upper: Histopathological examination six months after BNCT, right lower: Gd- and T2-MRI 4.5 years after BNCT.

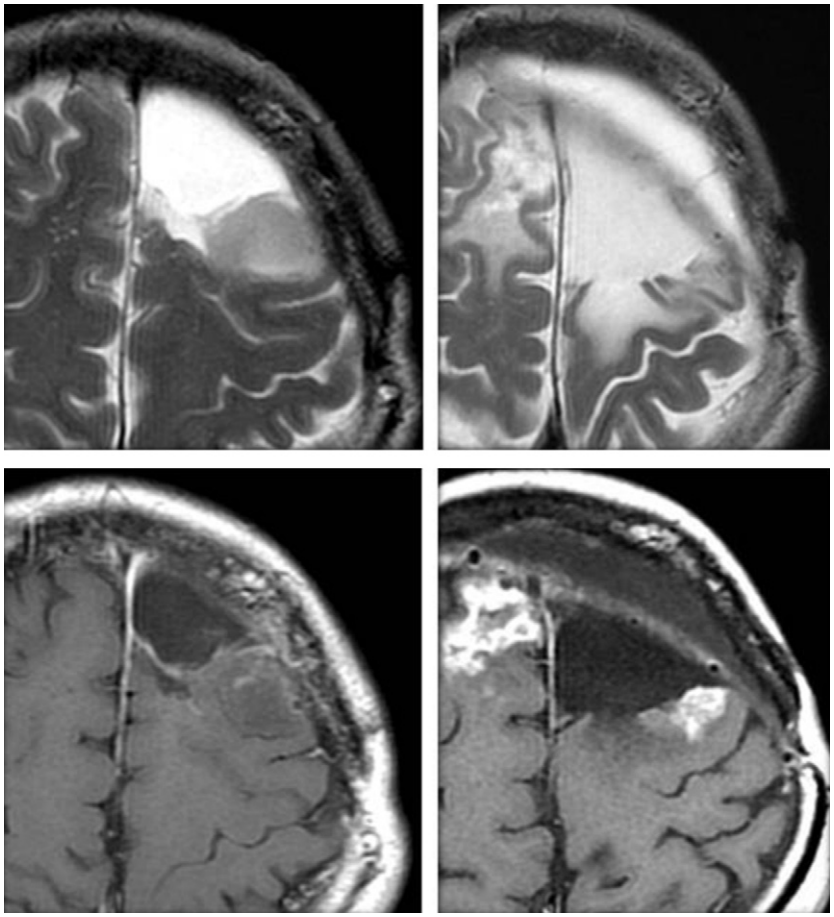

Fig. 2. Case 2: right frontal GBM 33-year-old female. Left: Gd- and T2-MRI before BNCT, middle: Gd- and T2-MRI four years after BNCT.

necrosis after BNCT, and three patients received surgical treatment within one year after BNCT.

According to the adverse effect, all five patients demonstrated radiographical radiation necrosis on follow-up MRI. There were four symptomatic patients, who were all treated with IO-BNCT. One patient had no symptom, who was treated with NO-BNCT. Median survival time (MST) and two-year survival time for early period of IO-BNCT (1998–2000) were 15.5 months and 0%,

Table 1
Minimal GTV (gross tumor volume) dose.

	Long-survivors	Non-long-survivors	*P* value
Physical dose (Gy)	21.2 ± 8.3	14.2 ± 5.3	0.03
Weighted dose (Gy(w))	59.7 ± 22.6	43.1 ± 12.9	0.04

Table 2
Minimal CTV (clinical tumor volume) dose.

	Long-survivors	Non-long-survivors	*P* value
Physical dose (Gy)	13.1 ± 9.9	8.7 ± 4.1	0.14
Weighted dose (Gy(w))	38.9 ± 27.0	28.1 ± 11.1	0.18

respectively, and for late period of IO-BNCT (2001–2004) were 19.5 months and 32.7%, respectively. These for NO-BNCT were 24.2 months and 44.4%, respectively and for all BNCT patients were 19.5 months and 19.9%, respectively.

3.1. Illustrative case

3.1.1. Case 1: right frontal GBM

This 48-year-old man with a history of dull headache and left hemiparesis was admitted at another institute. The initial MRI demonstrated a large, ring-enhanced mass in the right frontal lobe. He underwent craniotomy and partial resection of tumor. IO-BNCT was done on December 14, 2004. He received an intravenous infusion of 111 mg/kg BSH 12 h before neutron radiation. On retrospective analysis, the minimal physical and weighted dose to the GTV were 23.8 Gy and 66.6 Gy(w), respectively. These to the CTV were 8.6 Gy and 28.6 Gy(w), respectively. He experienced no symptoms after BNCT. A follow-up MRI study performed 6 months later showed an enlarged cyst formation with a mild wall enhancement. Based on a diagnosis of delayed radiation necrosis he again underwent craniotomy to remove the abnormal brain tissue. Histopathological examination of these specimens showed only necrosis without any tumor cells. On September 2009, 1792 days after surgery and 1749 days after BNCT, he died due to acute myocardial infarction.

3.1.2. Case 2: left frontal GBM

This 33-year-old woman with a history of generalized convulsion was admitted at our institute on November 2005. The initial MRI demonstrated hyperintensity on T2-WI MRI in left frontal motor area without abnormal enhancement on Gd-MRI. She underwent craniotomy and gross total removal of tumor on November 22, 2005. She was diagnosed as diffuse astrocytoma (grade II) histopathologically. One year after operation, a follow-up MRI demonstrated tumor recurrence at primary site. Salvage surgery was done on November 13, 2006. Histopatholigical examination showed glioblatoma. She underwent NO-BNCT on January 16, 2007. She received an intravenous infusion of 100 mg/kg BSH 12 h before and 250 mg/kg BPA 1 h before neutron irradiation. On retrospective analysis, the minimal physical and weighted dose to the GTV were 8.1 Gy and 26.4 Gy(w), respectively. These to the CTV were 4.1 Gy and 13.7 Gy(w), respectively. She experienced no symptoms after BNCT. A follow-up MRI study demonstrated abnormal enhancement area in contra-lateral and ipsi-lateral frontal lobe, however, she suffered from no neurological deficits. She is still alive 1430 days after surgery and 1384 days after BNCT (October 31, 2010).

4. Discussion

Among 23 GBM patients treated with BNCT, there were five patients who survived more than three years after diagnosis without additional chemotherapy such as a temozolomide. There were four and one patients treated with IO- and NO-BNCT, respectively. BNCT radiation dose of late period of IO-BNCT (2001–2004) was 1.1–1.3 times higher than that of early period of IO-BNCT (1998–2001). This dose escalation contributed to the improvement in clinical outcome. The median survival time of early and late period of IO-BNCT were 15.3 and 19.5 months, respectively. Two-year survival rate were 0 and 37.9%, respectively. There was a significant statistical correlation between the maximal minimal and mean GTV dose and median survival time. On the other hand, this dose escalation resulted in high frequency of radiation injury after BNCT (Kageji et al., 2006). We have reported histopathological findings in autopsied glioblatoma three patients treated by mixed neutron beam BNCT. None had local tumor regrowth at the primary site. Two patients demonstrated residual tumor cells around tumor cavity, one patient demonstrated wide-spread tumor invasion into contra-lateral hemisphere, two patients demonstrated CSF dissemination. The minimal GTV dose ranged from 14.7 to 15.3 Gy as a physical dose (Kageji et al., 2004).

In this study, we analyzed the BNCT radiation dose between long-survivors (more than three years) and non-long-survivors (below three years) in patients with glioblatoma treated with single treatment of BNCT. The GTV dose had significant statistical differences between long- and non-long-survivors, however, the CTV dose had no significant statistical differences. For long survival, the optimal minimal GTV dose was 21 Gy as a physical dose, and 60 Gy(w) as a weighted dose. These BNCT radiation dose leads to symptomatic radiation injury. We have shifted from IO-BNCT to NO-BNCT in 2006 to improve clinical outcome. There are many advantages in NO-BNCT; less invasive treatment to patient, less adverse effect, possibility to undergo multi-staged treatment. On the other hand, BNCT radiation dose of NO-BNCT may be insufficient for long survival of glioblatoma as a single treatment of BNCT. For further improvement of clinical outcome of NO-BNCT, the following should be considered: fractionated BNCT, additional conventional radiation after BNCT and following intensive chemotherapy such as temozolomide.

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