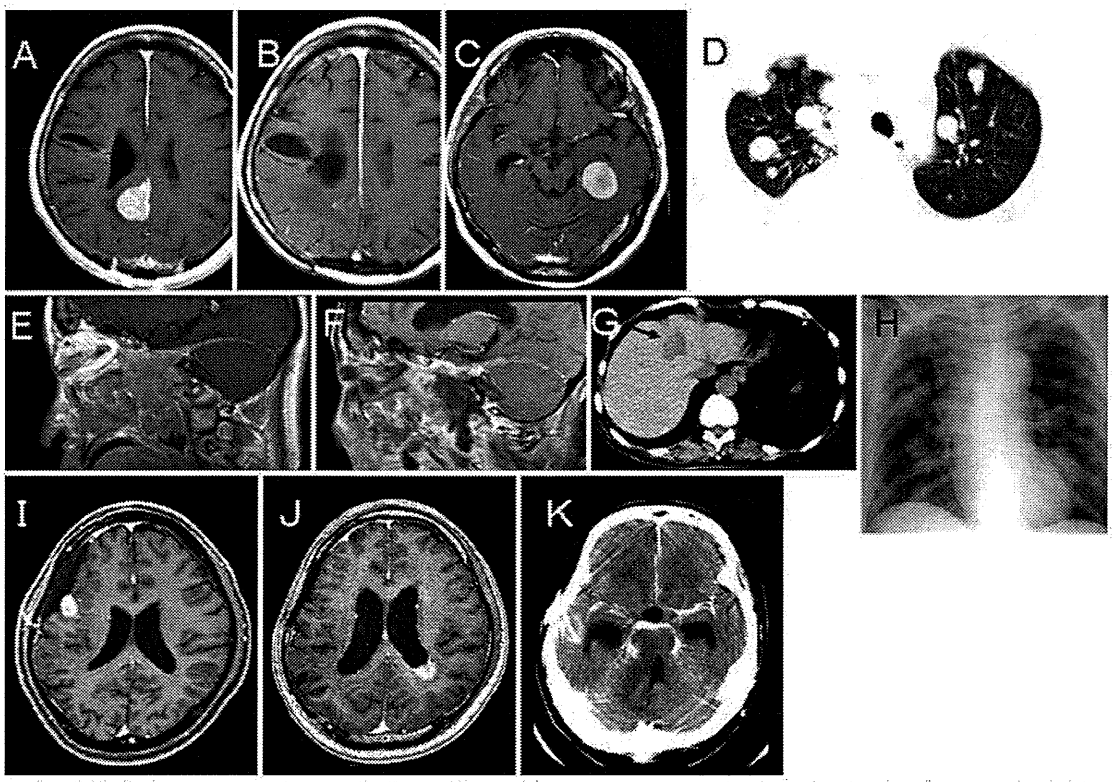

Fig. 3. Typical images of systemic metastasis, intracranial recurrence outside the field of neutron irradiation, and CSF dissemination. **A–D:** Case 13 (anaplastic meningioma). Axial contrast-enhanced MR images obtained prior to BNCT (A) and 33 months after BNCT (B and C), and plain chest CT scan obtained 39 months after BNCT (D). The MRI (C) shows intracranial recurrence out of the field of neutron irradiation. The chest CT scan (D) shows lung metastasis of the meningioma. This patient died due to dyspnea. The patient had already suffered from metastasis of the meningioma at the left clavicle prior to BNCT. **E–H:** Case 7 (sarcoma transformed from anaplastic meningioma). Sagittal contrast-enhanced MR image obtained prior to BNCT (E), sagittal contrast-enhanced MR image (F), plain abdominal axial CT scan (G), and chest radiograph (H) obtained 7 months after BNCT. The original, very large tumor was well controlled by BNCT, but lung and liver metastasis occurred. This patient died due to dyspnea. The *black arrow* (G) shows liver metastasis. **I–K:** Case 11 (anaplastic meningioma). Axial contrast-enhanced MR images obtained prior to BNCT (I) and 7 months after BNCT (J), axial contrast-enhanced CT scan (K) obtained 10 months after BNCT. The original tumor was controlled well, but CSF dissemination with untreatable hydrocephalus occurred.

Historically, conventional EBRT was first used to treat high-grade meningiomas, but with unsatisfactory results.[20] In our series, the original high-grade meningiomas were not controlled locally by EBRT alone. Thereafter, SRS was used for the treatment of high-grade meningiomas, as reported in the literature.[13,27,29,31] The gross tumor volume treated by SRS in these studies was relatively small in comparison with that in our series. Additionally, in our series, 9 patients had already received repetitive SRS but experienced recurrence nonetheless. The typical treatment failure pattern of high-grade meningiomas by SRS in our series was marginal recurrence at the SRS fields. Even for these SRS-refractory cases, BNCT was able to provide good local tumor control.

Particle radiotherapies using proton beams[2,6,14,26,30,33] and carbon ion beams[8,30] have been more recently applied

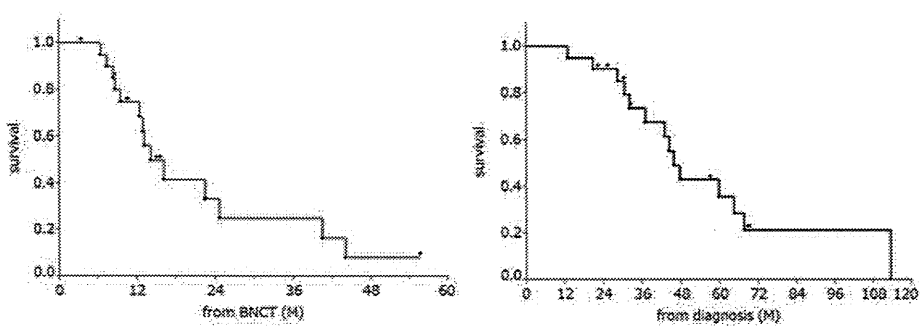

Fig. 4. Graphs of Kaplan-Meyer survival curves after BNCT **(left)** and diagnosis **(right)**. The median survival times after BNCT and diagnosis were 14.1 months (95% CI 8.6–40.4 months) and 45.7 months (95% CI 32.4–70.7 months), respectively.

to cases of high-grade meningioma. Again, it is very difficult to compare our data to the data from particle radiotherapies. First, almost all reported series, including our own, have comprised a limited number of cases. The protocols have varied as well: in some studies, particle therapy was applied just after surgery as the initial radiotherapy, and in others it was applied at recurrence. The applied doses varied and in some trials, particle radiation was followed by fractionated EBRT. In addition, the data on tumor shrinkage after particle irradiation have been scarce. There has been only 1 preliminary report addressing this subject, and the results indicated no prominent early tumor shrinkage using proton and carbon ion beams for the treatment of high-grade meningiomas.[30]

One of the advantages of BNCT is that the radiation field may be planned rather more ambiguously than in SRS and other particle radiotherapies. This merit of BNCT might decrease recurrence in the peri-irradiated field in comparison with other radiation techniques, even with the same absorbed dose as described as "Gy-Eq." Encouragingly, almost all masses in our series responded well, with rapid shrinkage after BNCT (Figs. 2 and 3), as also reported elsewhere.[23] This rapid shrinkage might contribute to the prompt recovery of symptoms in some cases. Our patient in Case 1 became ambulatory 1 week after BNCT, and our patient in Case 7 experienced relief from facial pain within 2 weeks of BNCT, as reported previously.[23,32]

In BNCT, most potent antitumor effects are caused by particles, and we applied 33.3 Gy-Eq and 73.4 Gy-Eq for tumor tissue as minimum and maximum 1-time tumor doses, respectively (Table 1). In the literature on particle radiation, some clinical trials have used proton or carbon particle doses between 18 Gy-Eq and 56 Gy-Eq with fractionation.[8,33] The difference in tumor shrinkage between α and lithium particles and other particles such as carbon and protons may be ascribed to the difference of linear energy transfer. The linear energy transfer of α and lithium particles is higher than that of both protons and carbon particles. It is widely accepted that high linear energy transfer particles have greater biological effects than low linear energy transfer particles;[1,3] of course, there might be other causes. For example, in BNCT a large dose can be delivered at a single time, while other particles are usually applied with fractionation and additional low linear energy transfer EBRT. Because of this difference in protocol, other particles might have less impact on tumor shrinkage.

With respect to adverse effects of BNCT, we experienced 6 cases of symptomatic radiation injury among our 20 cases. One instance was the occurrence of subacute brain swelling after BNCT, as reported previously,[23] while the other 5 cases appeared to show radiation necrosis. Because all cases were introduced to our institute after intensive radiotherapies prior to BNCT, radiation necrosis may have been inevitable, despite the tumor-selective nature of BNCT. Recently, we applied BNCT to a patient with a high-grade meningioma who had never been treated with any radiotherapy, and are now observing this case carefully. Bevacizumab has shown potent effects treating symptomatic radiation necrosis in the brain,[12,18] and we have applied this drug for symptomatic radiation necrosis after BNCT for malignant gliomas.[11] This strategy should be applicable and effective for the treatment of radiation necrosis after BNCT for high-grade meningiomas.

We should emphasize that we found pseudoprogression after BNCT in at least 3 of our 20 high-grade meningioma cases. As we described previously,[22] this phenomenon could itself be an indicator of how promising and intensive the effects of this treatment are.

Conclusions

Boron neutron capture therapy is a new treatment concept and method that has already been used on malignant gliomas, including glioblastomas. Our study suggests that high-grade meningiomas may be an even better candidate for BNCT than those lesions. The meningiomas in our series were somewhat superficial (located on the surface of the brain), except for some specific situations at the skull base, which is advantageous to neutron penetration.

With regard to BPA accumulation, high-grade meningiomas showed a good ratio of tumor to normal brain, even compared with malignant gliomas (Table 1). In addition, judging from the rapid shrinkage of the mass, our assumption about the compound biological effectiveness of BPA for high-grade meningioma—which was assumed to be equal to that of glioblastoma—might have been an underestimation; the real value might be higher than that for glioblastoma. If we can apply BNCT for high-grade meningioma as the initial radiotherapy or at least at the first recurrence, rather than at such advanced stages, more favorable results than those described in our study might be obtained, such as avoiding systemic metastasis or out-of-field recurrence.

Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: Miyatake, Kawabata, Ono. Acquisition of data: Miyatake, Kawabata, Hitramatsu. Analysis and interpretation of data: Miyatake, Kawabata, Hitramatsu. Drafting the article: Miyatake, Kawabata. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Miyatake. Study supervision: Miyatake, Kuroiwa, Ono.

References

1. Barendsen GW: RBE-LET relationships for different types of lethal radiation damage in mammalian cells: comparison with DNA dsb and an interpretation of differences in radiosensitivity. **Int J Radiat Biol 66:**433–436, 1994
2. Boskos C, Feuvret L, Noel G, Habrand JL, Pommier P, Alapetite C, et al: Combined proton and photon conformal radiotherapy for intracranial atypical and malignant meningioma. **Int J Radiat Oncol Biol Phys 75:**399–406, 2009
3. Broerse JJ, Barendsen GW, van Kersen GR: Survival of cultured human cells after irradiation with fast neutrons of dif-

ferent energies in hypoxic and oxygenated conditions. **Int J Radiat Biol Relat Stud Phys Chem Med 13:**559–572, 1968
4. Chamberlain MC: The role of chemotherapy and targeted therapy in the treatment of intracranial meningioma. **Curr Opin Oncol 24:**666–671, 2012
5. Chamberlain MC, Glantz MJ: Cerebrospinal fluid-disseminated meningioma. **Cancer 103:**1427–1430, 2005
6. Chan AW, Bernstein KD, Adams JA, Parambi RJ, Loeffler JS: Dose escalation with proton radiation therapy for high-grade meningiomas. **Technol Cancer Res Treat 11:**607–614, 2012
7. Coderre JA, Morris GM: The radiation biology of boron neutron capture therapy. **Radiat Res 151:**1–18, 1999
8. Combs SE, Hartmann C, Nikoghosyan A, Jäkel O, Karger CP, Haberer T, et al: Carbon ion radiation therapy for high-risk meningiomas. **Radiother Oncol 95:**54–59, 2010
9. Enam SA, Abdulrauf S, Mehta B, Malik GM, Mahmood A: Metastasis in meningioma. **Acta Neurochir (Wien) 138:**1172–1178, 1996
10. Farr LE, Sweet WH, Robertson JS, Foster CG, Locksley HB, Sutherland DL, et al: Neutron capture therapy with boron in the treatment of glioblastoma multiforme. **Am J Roentgenol Radium Ther Nucl Med 71:**279–293, 1954
11. Furuse M, Kawabata S, Kuroiwa T, Miyatake SI: Repeated treatments with bevacizumab for recurrent radiation necrosis in patients with malignant brain tumors: a report of 2 cases. **J Neurooncol 102:**471–475, 2011
12. Gonzalez J, Kumar AJ, Conrad CA, Levin VA: Effect of bevacizumab on radiation necrosis of the brain. **Int J Radiat Oncol Biol Phys 67:**323–326, 2007
13. Hakim R, Alexander E III, Loeffler JS, Shrieve DC, Wen P, Fallon MP, et al: Results of linear accelerator-based radiosurgery for intracranial meningiomas. **Neurosurgery 42:**446–454, 1998
14. Hug EB, Devries A, Thornton AF, Munzenride JE, Pardo FS, Hedley-Whyte ET, et al: Management of atypical and malignant meningiomas: role of high-dose, 3D-conformal radiation therapy. **J Neurooncol 48:**151–160, 2000
15. Imahori Y, Ueda S, Ohmori Y, Kusuki T, Ono K, Fujii R, et al: Fluorine-18-labeled fluoroboronophenylalanine PET in patients with glioma. **J Nucl Med 39:**325–333, 1998
16. Imahori Y, Ueda S, Ohmori Y, Sakae K, Kusuki T, Kobayashi T, et al: Positron emission tomography-based boron neutron capture therapy using boronophenylalanine for high-grade gliomas: part I. **Clin Cancer Res 4:**1825–1832, 1998
17. Jääskeläinen J, Haltia M, Servo A: Atypical and anaplastic meningiomas: radiology, surgery, radiotherapy, and outcome. **Surg Neurol 25:**233–242, 1986
18. Levin VA, Bidaut L, Hou P, Kumar AJ, Wefel JS, Bekele BN, et al: Randomized double-blind placebo-controlled trial of bevacizumab therapy for radiation necrosis of the central nervous system. **Int J Radiat Oncol Biol Phys 79:**1487–1495, 2011 (Erratum in **Int J Radiat Oncol Biol Phys 84:**6, 2012)
19. Locher G: Biological effects and therapeutic possibilities of neutrons. **Am J Roentgenol Radium Ther 36:**1–13, 1936
20. Mahmood A, Caccamo DV, Tomecek FJ, Malik GM: Atypical and malignant meningiomas: a clinicopathological review. **Neurosurgery 33:**955–963, 1993
21. Miyatake S, Kawabata S, Kajimoto Y, Aoki A, Yokoyama K, Yamada M, et al: Modified boron neutron capture therapy for malignant gliomas performed using epithermal neutron and two boron compounds with different accumulation mechanisms: an efficacy study based on findings on neuroimages. **J Neurosurg 103:**1000–1009, 2005
22. Miyatake S, Kawabata S, Nonoguchi N, Yokoyama K, Kuroiwa T, Matsui H, et al: Pseudoprogression in boron neutron capture therapy for malignant gliomas and meningiomas. **Neuro Oncol 11:**430–436, 2009
23. Miyatake S, Tamura Y, Kawabata S, Iida K, Kuroiwa T, Ono K: Boron neutron capture therapy for malignant tumors related to meningiomas. **Neurosurgery 61:**82–91, 2007
24. Morris GM, Coderre JA, Hopewell JW, Micca PL, Fisher C: Boron neutron capture irradiation of the rat spinal cord: effects of variable doses of borocaptate sodium. **Radiother Oncol 39:**253–259, 1996
25. Morris GM, Coderre JA, Micca PL, Fisher CD, Capala J, Hopewell JW: Central nervous system tolerance to boron neutron capture therapy with p-boronophenylalanine. **Br J Cancer 76:**1623–1629, 1997
26. Noël G, Habrand JL, Mammar H, Haie-Meder C, Pontvert D, Dederke S, et al: Highly conformal therapy using proton component in the management of meningiomas. Preliminary experience of the Centre de Protonthérapie d'Orsay. **Strahlenther Onkol 178:**480–485, 2002
27. Ojemann SG, Sneed PK, Larson DA, Gutin PH, Berger MS, Verhey L, et al: Radiosurgery for malignant meningioma: results in 22 patients. **J Neurosurg 93 (Suppl 3):**62–67, 2000
28. Palma L, Celli P, Franco C, Cervoni L, Cantore G: Long-term prognosis for atypical and malignant meningiomas: a study of 71 surgical cases. **J Neurosurg 86:**793–800, 1997
29. Pollock BE, Stafford SL, Link MJ, Garces YI, Foote RL: Stereotactic radiosurgery of World Health Organization grade II and III intracranial meningiomas: treatment results on the basis of a 22-year experience. **Cancer 118:**1048–1054, 2012
30. Rieken S, Habermehl D, Haberer T, Jaekel O, Debus J, Combs SE: Proton and carbon ion radiotherapy for primary brain tumors delivered with active raster scanning at the Heidelberg Ion Therapy Center (HIT): early treatment results and study concepts. **Radiat Oncol 7:**41, 2012
31. Stafford SL, Pollock BE, Foote RL, Link MJ, Gorman DA, Schomberg PJ, et al: Meningioma radiosurgery: tumor control, outcomes, and complications among 190 consecutive patients. **Neurosurgery 49:**1029–1038, 2001
32. Tamura Y, Miyatake S, Nonoguchi N, Miyata S, Yokoyama K, Doi A, et al: Boron neutron capture therapy for recurrent malignant meningioma. Case report. **J Neurosurg 105:**898–903, 2006
33. Weber DC, Schneider R, Goitein G, Koch T, Ares C, Geismar JH, et al: Spot scanning-based proton therapy for intracranial meningioma: long-term results from the Paul Scherrer Institute. **Int J Radiat Oncol Biol Phys 83:**865–871, 2012

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特集　グリオーマ　新しい時代の到来

腫瘍細胞選択的粒子線治療「ホウ素中性子捕捉療法」と抗血管新生薬による症候性脳放射線壊死の治療

宮武　伸一[1)]

1）大阪医科大学医学部脳神経外科

Cell-selective Particle Radiation, Boron Neutron Capture Therapy and Treatment of Symptomatic Radiation Necrosis in the Brain by Anti-angiogenic Agent

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Boron neutron capture therapy (BNCT) has been advocated as a novel particle radiation therapy for malignant tumors that targets tumor cells biologically. Since 2002, we have applied this unique radiotherapy for 133 malignant gliomas and malignant meningiomas at our institution. In addition, we recently applied anti-angiogenic agents aggressively for intractable symptomatic radiation necrosis in the brain.

Here is our latest comprehensive data regarding these unique treatments, including those I presented at the 32nd annual meeting of the Japanese Neurosurgical Congress, along with some new findings.

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Key words : bevacizumab, boron neutron capture therapy (BNCT), positron emission tomography (PET), radiation necrosis

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はじめに

Boron neutron capture therapy（以下 BNCT）は原理上腫瘍に対する細胞選択的照射が可能な唯一の放射線治療法である．ホウ素（^{10}B）化合物を投与し，その後，熱中性子もしくは熱外中性子を照射する．ホウ素化合物自体には細胞毒性はなく，また中性子の殺細胞効果もきわめて小さいが，ホウ素同位体^{10}B 原子核は中性子を捕獲し，きわめて線エネルギー付与（粒子が 1 μm 運動する間に周囲に付与するエネルギー：keV/μm）の高いヘリウム原子核（α粒子）とリチウム反跳核をそれぞれ，9 μm と 4 μm という，細胞 1 個に相当する距離に放出し，その細胞を破壊する細胞選択的な粒子線治療ともいえる（Fig. 1）[3]．すなわち殺細胞効果はホウ素中性子捕獲反応の生じた細胞に限局され，隣接する細胞には影響を及ぼさない．そこで，ホウ素化合物を腫瘍に選択的に集積できれば，腫瘍選択的な細胞破壊が可能となる．

本稿では，まず BNCT 時にその適応決定，線量 simulation に用いる F-BPA-PET を紹介し，次いで悪性神経膠腫に対する治療効果，悪性髄膜腫に対する治療効果，F-BPA-PET による治療効果の判定や放射線壊死，pseudoprogression の鑑別を紹介する．さらには原子炉に代わる新規中性子源として開発してきた小型加速器による治験を紹介する．最後に高線量放射線治療の宿命ともいえ

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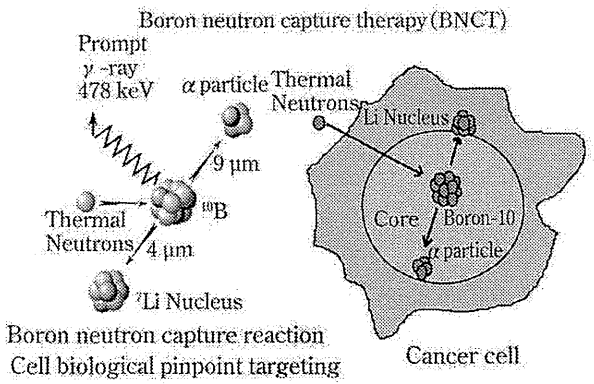

Fig. 1 Principle of BNCT

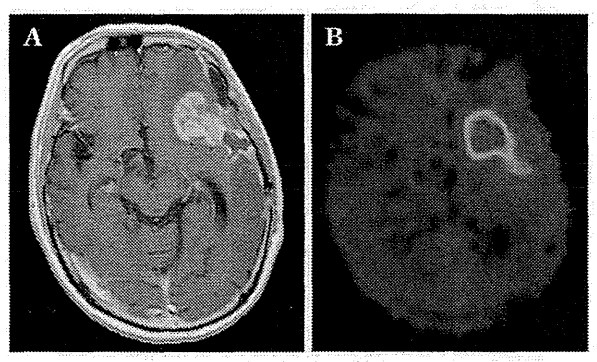

Fig. 2 Typical F-BPA-PET findings in glioblastoma multiforme (GBM)
A: T1-Gd enhanced MRI revealed a left frontal mass. **B**: F-BPA-PET imaging showed marked BPA accumulation not only in the enhanced area but also in the surrounding brain. The lesion/normal brain ratio of the tracer uptake in this case was 7.1.

る，脳放射線壊死に対する抗血管新生薬による治療法とその薬事申請への行程を紹介する．

F-BPA-PET

BNCT における治療用化合物 BPA（boronophenylalanine）を用いた PET 検査を中性子照射に先立って行う．BPA は文字通りホウ素化した phenylalanine であり，腫瘍において亢進したアミノ酸代謝を利用し，腫瘍内に能動的かつ選択的に集積される．フッ素ラベルした BPA をトレーサとして利用することにより，PET により腫瘍内および脳内 BPA 濃度が推測され，治療の適応決定および照射線量が simulation できる．**Fig. 2** に BPA-PET による BPA の取り込みを示す．この症例では左前頭葉部腫瘍は反対側正常脳に比べて，7.1 倍のトレーサの集積を示している．この PET が示す情報は大きく，2 つの情報が存在する．1 つは 7.1 倍という数字は，同一部位に腫瘍細胞と正常細胞が存在すれば（浸潤部領域にそのような situation が想像できる），腫瘍細胞は正常細胞の 7.1 倍の粒子線を吸収することを示す．もう 1 つの情報は，造影 MRI に比較して，その外側にもトレーサの集積を認めることより，造影域より外側に浸潤している細胞にも targeting できていることを物語っている[10]．

悪性神経膠腫に対する BNCT の効果

悪性黒色腫とともに最も初期より BNCT が適応されてきた疾患が悪性神経膠腫であった．われわれは再発悪性神経膠腫に BNCT を適応し，すべての症例で画像上顕著な効果を認めた[7)10)]．また，新規診断膠芽腫にも積極的に BNCT を適応し，化学療法なしに良好な成績を収めている[8)]．この経験をもとに，現在 BNCT 後に追加 X 線外照射および temozolomide を併用した，新規診断膠芽腫に対する多施設共同研究を厚生労働科学研究費のサポートをいただき，展開中である．

初発膠芽腫に対する BNCT の効果および問題点を示す症例を **Fig. 3** として提示する．左側脳室三角部近傍の膠芽腫である．手術による部分摘出の後，BNCT を施行した．BNCT 施行前，施行 8 カ月後の頭部 MRI および脊髄 MRI を A，B，C として提示している．BNCT は良好な局所制御を示しているが，脊髄髄腔内播種をきたし，この症例を亡くしている．われわれの BNCT の経験では，このように局所制御は比較的良好であるが，およそ半分の症例は髄腔内播種で亡くしている．今後の課題と考えている．

すでに放射線治療歴を有する再発悪性神経膠腫に対しても，本治療法は細胞選択性を有するので，積極的な照射を行ってきた．再発神経膠腫に対する RPA 分類を用いて[2)]，BNCT の成績と既存治療法の成績を比較すると，予後不良群でその生存期間中央値を有意に延長している[13)]．しかしながら，たとえば **Fig. 2** に示した症例では，病変と正常脳のトレーサの集積比が 7.1 倍と高値を示すが，逆に考えると正常脳は腫瘍の 1/7.1 の粒子線を被曝する．再発例の場合にはすでに許容線量限界に近い放射線治療が施行されているので，BNCT といえども，脳放射線壊死が問題となる．この点に関しては後述の抗血管新生療法を展開している．

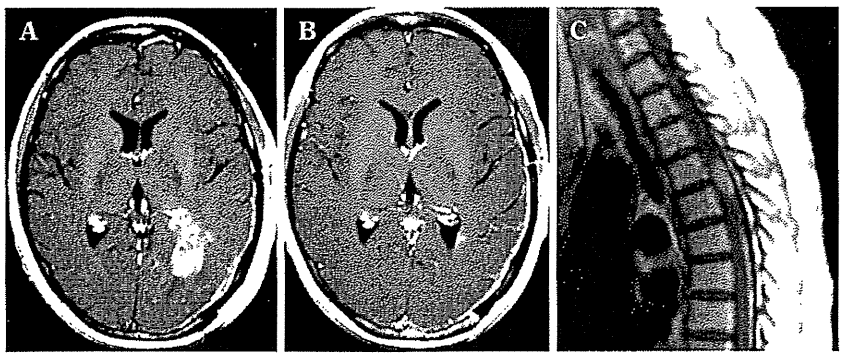

Fig. 3 Periodic Gd-enhanced MRI findings of a GBM case treated by BNCT. A newly diagnosed GBM case in which the left trigonal lesion was treated by BNCT.
A: Brain MRI, prior to BNCT. B: Brain MRI, 8 months after BNCT. C: Spinal MRI, 8 months after BNCT, showing CSF dissemination of the lesion at the spinal cord.

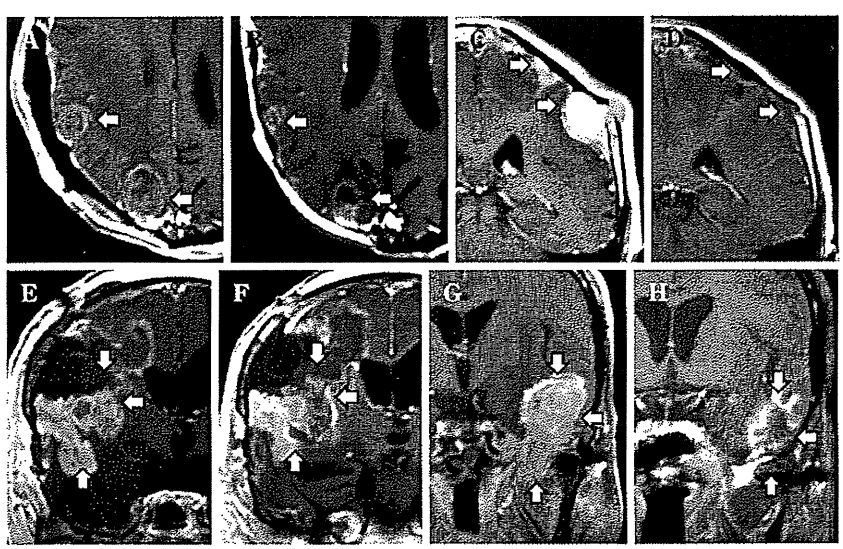

Fig. 4 Typical MRI changes of malignant meningiomas treated by BNCT
A, B: Prior to BNCT and 3 months after BNCT of a anaplastic meningioma.
C, D: Prior to BNCT and 4 months after BNCT of a anaplastic meningioma.
E, F: Prior to BNCT and 5 months after BNCT of an anaplastic meningioma.
G, H: Prior to BNCT and 4 months after BNCT of a rhabdoid meningioma.

高グレード髄膜腫に対する BNCT の効果

高グレード髄膜腫（high grade meningioma：HGM）は手術，定位放射線治療を行っても，その予後は悪い[6)18)]．ことに WHO grade 3 に属する anaplastic meningioma の予後は悪い．われわれは世界に先駆けて，これら HGM に対しても積極的に BNCT を適応してきた[11)19)]．Fig. 4 に anaplastic meningioma 3 例，rhabdoid meningioma 1 例の BNCT 前後の MRI を示す．この 4 例以外でもすべての症例で画像上顕著な腫瘍縮小効果を経験している．われわれの施設に紹介をいただく症例はすべて，複数回の手術，X 線外照射，定位放射線治療等が施行され，それでも制御不能な治療不応症例であるが，良好な局所制御を認めている．2011 年 9 月までに治療を終え，その後 1 年以上の経過を観察しえた 20 例では，局所再発は 4 例で認めたのみであるが，多くの症例を BNCT 後に失っ

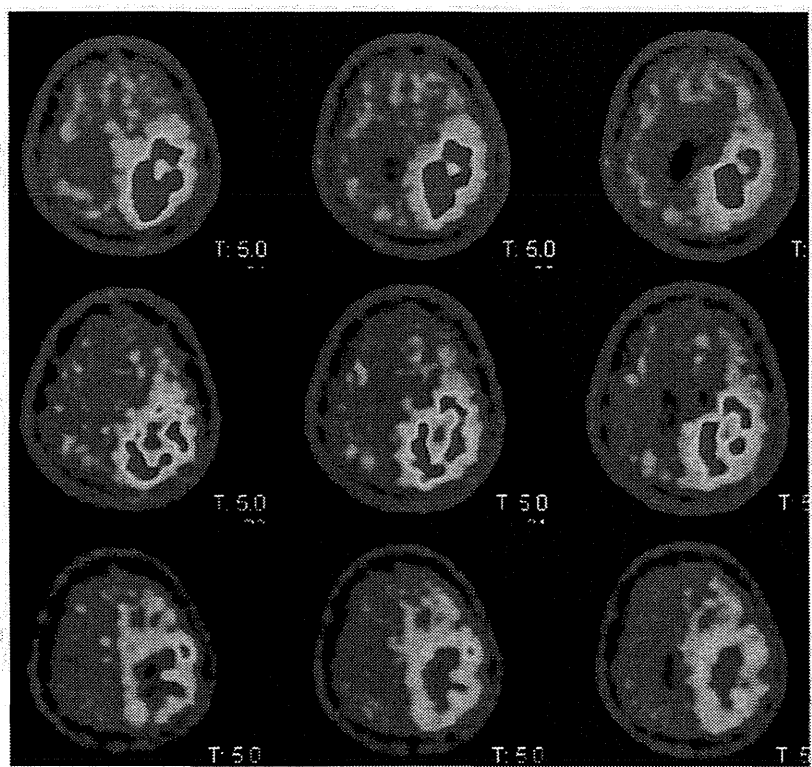

Fig. 5 Periodic change of F-BPA-PET imaging of a recurrent anaplastic astrocytoma treated by BNCT
A：Prior to BNCT, the lesion/normal brain ratio was 7.0.
B：3 months after BNCT, the lesion/normal brain ratio was 3.5.
C：9 months after BNCT, the lesion/normal brain ratio was 2.5.

ている．このうちの7例は照射野外再発，6例が全身転移によるものであり，3例が髄腔内播種による難治性水頭症による頭蓋内圧亢進により失っており，この疾患のコントロールの困難さを痛感している（論文印刷中）．これらはいずれも疾患が治療時にはすでに進行していることに起因しており，これを回避するには初期の再発時にBNCTを行う以外に有効な手立てはないと考えている．

F-BPA-PETによる治療効果判定

Fig. 5に再発神経膠腫（anaplastic astrocytoma）のBNCT前，BNCT 3カ月後，9カ月後のF-BPA-PETを示す．BNCT 3カ月後に本PETを施行した理由は若干の浮腫，造影域の拡大を認めたため，腫瘍のprogressionかpseudoprogressionかの判断を行うために施行したものであり，このPETにより病変/正常脳比の低下を確認してpseudoprogressionと判断し，経過を観察している．9カ月後のPETではさらにこの比が低下を示しており，良好な治療効果を確認している．本症例は前述の再発神経膠腫に対するRPA分類ではクラス3に分類され，再発時治療後の生存期間中央値は文献上，わずか3.8カ月と報告されている．本症例は，本稿準備時すでにBNCT後11カ月が経過しているが再発の徴候は認めていない．われわれは本PETを腫瘍再発と脳放射線壊死の鑑別[9]やpseudoprogressionとtrue progressionの鑑別に用いている[12]．

加速器中性子源によるBNCT

上述のBNCTはすべて原子炉からの中性子を用いたBNCTの成績である．原子炉を用いる限り，またホウ素化合物も医薬品としてのGMPグレードを開発しない限り，BNCTは医療としては認知されない．数年前にわれわれが厚生労働省に本治療を当時の高度先進医療に申請した折から，この点は指摘されており，大きな宿題であった．この要求に応えるため，某製薬メーカーと医療機器開発メーカーの主導により，加速器中性子源とGMPグレードBPAの開発が行われ，著者が治験責任医師とな

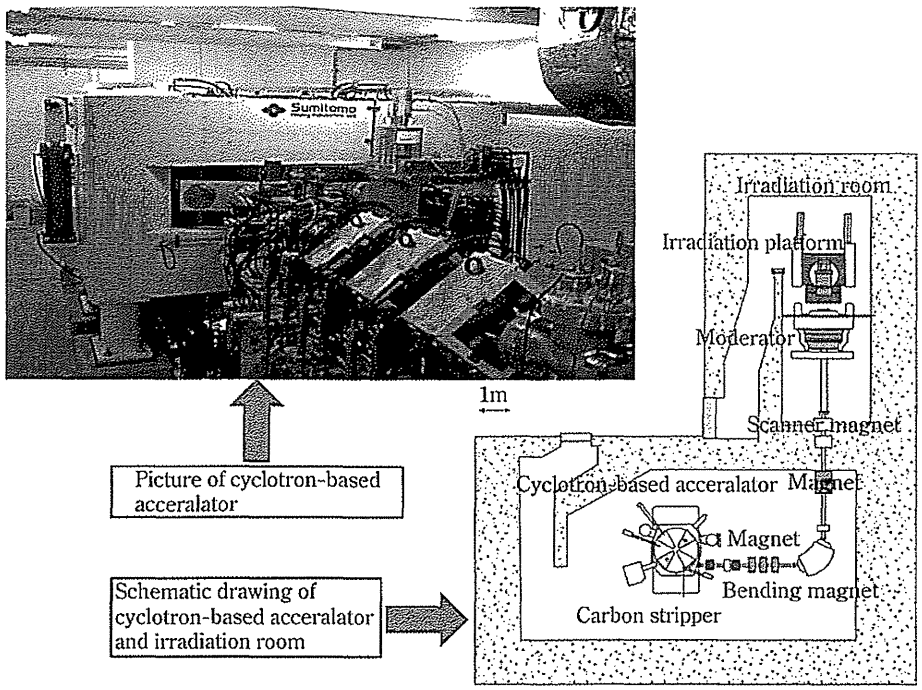

Fig. 6 Photograph of the cyclotron-based accelerator for neutron generation and a schematic drawing of the total irradiation room

り，再発悪性神経膠腫を対象として，第 1 相臨床試験（治験）を開始している．Fig. 6 にサイクロトロン型小型加速器中性子源（実写）とその治療室の見取り図を提示する．原子炉に比してはるかに小型化された加速器の実寸が見て取れる．本治験が成功すれば院内 BNCT が可能となり，薬事承認を目指して臨床試験を遂行中である．

症候性脳放射線壊死に対するベバシズマブの静脈内投与による治療

BNCT や強度変調放射線治療あるいは定位放射線治療等の高線量放射線治療は着実に，頭蓋内悪性腫瘍の治療成績を向上させている[5)8)17)20)]．一方でこれら高線量，高精度放射線治療の適応により，症候性脳放射線壊死が問題となっている．症候性脳放射線壊死に対してはステロイドホルモン等が経験的に投与されてはいるが，有効な治療法は確立されていない．

脳放射線壊死組織の手術摘出標本の検討から，放射線壊死における脳浮腫の原因が壊死巣周囲の脆弱な血管新生であり，さらにその原因が血管内皮増殖因子（vascular endothelial growth factor：VEGF）の過剰産生にあることをわれわれは解明した[16)]．そこでこの知見をもとに，抗 VEGF 抗体製剤であるベバシズマブを症候性脳放射線壊

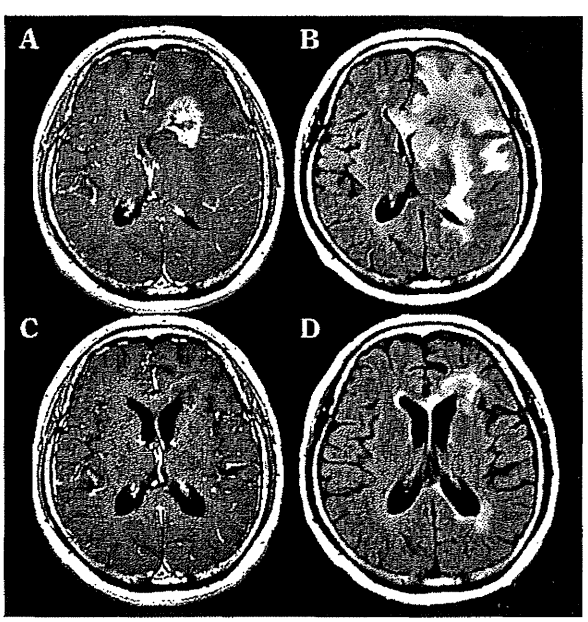

Fig. 7 Case of radiation necrosis successfully treated by bevacizumab. Radiation necrosis was due to repetitive SRSs for a metastatic brain tumor of uterus cancer.
A：Pre-treatment T1-Gd MRI. B：Pre-treatment FLAIR MRI. C：Post-treatment T1-Gd MRI. D：Post-treatment FLAIR MRI. A drastic decrease of Gd-enhancement and brain edema was observed by 6 cycles of bevacizumab treatment.

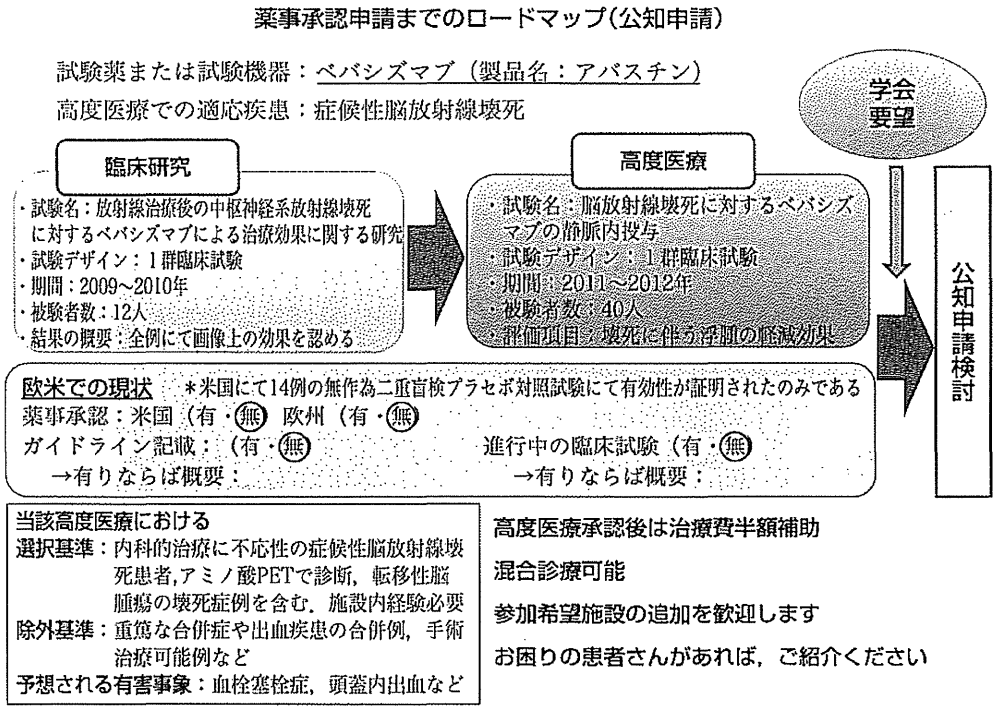

Fig. 8 Roadmap for obtaining permission for on-label use of bevacizumab for symptomatic radiation necrosis in the brain

死の症例に投与したところ，原因となる腫瘍の組織型や用いた放射線の種類を問わず，投与症例全例で顕著な脳浮腫および造影領域の縮小を認めた[4]．ここで問題となるのは放射線治療後に生じる脳浮腫の増悪が，腫瘍再発によるものかそれとも脳放射線壊死によるものかの鑑別を要する点である．われわれは上述の F-BPA-PET により，その鑑別を行っている[4)14)]．

これらの経験をもとに，厚生労働省に高度医療（第3項先進医療）として「症候性脳放射線壊死に対する核医学的診断とベバシズマブの静脈内投与による治療」を申請し，厚生労働科研費のサポートもいただき，2011年4月1日より40症例を登録予定数として全国16施設による多施設共同臨床研究を展開している[14)]．本臨床試験ではより多くの施設の参画を期待して，その診断には BPA-PET のほか，Met-PET も利用可としており，その詳細は拙稿をご参照いただきたい[14)]．われわれの経験症例を Fig. 7 に示す．

53歳女性．子宮体癌に対して全摘出術を受けた．その直後より脳内に多発性転移巣を認め，複数回の定位放射線治療を受けている．左前頭葉の病変には2度の定位照射が施行され，2度目の照射の2カ月後より，頭痛，失語症を発症し，ステロイドホルモンの投与によっても軽快せず，当科に紹介された．多発性の転移巣はいずれも BPA-PET で活動性を認めず，ことに左前頭葉の病変は病変/正常脳比 2.1 と算出され，われわれの定めた脳放射線壊死の基準値を満たし，ベバシズマブの投与を biweekly，5 mg/kg で行った．数回投与により症状は改善し，6回投与後の MRI では造影域，浮腫とも顕著に軽快している．

本稿準備中の2103年1月25日に予定症例数の40例の登録を終え，順調に臨床試験は進行している．臨床試験の成績をもとにした，われわれの描いている薬事承認を目指したロードマップを Fig. 8 に示す．症候性脳放射線壊死は重篤な機能予後および生命予後をきたす疾患ではあるが，母集団となる患者総数はそれほど多くなく，治験は組みにくい．そこで治験というプロセスを踏まずに薬事承認を目指すシステムとして，高度医療に思い至った次第である．本臨床試験にて万人が認めうる優れた成績を治めることができれば，各種学会からの学会要望を添えて，公知申請を行い，厚生労働省に薬事申請を認可していただくという戦略を厚生労働省の担当官との間で構築した．よっておよそ2年後に，日本定位放射線治療学会，日本脳神経外科学会，日本放射線腫瘍学会，日本核医学会からの学会要望がいただけるよう，臨床試

験を行っている次第である[14]．

最後に再発悪性神経膠腫に対して，BNCT を行うと，しばしば pseudoprogression に遭遇する[12]．この pseudoprogression は intensive treatment の証として認識されているが[1]，多くの場合無症候であり，ステロイドホルモンの投与で対応可能であることが多い．最近われわれは再発悪性神経膠腫に対しての BNCT 後に symptomatic pseudoprogression となった症例に，ベバシズマブを投与したところ，劇的な改善を経験しており，本治療の新たな展開と考えている[15]．Pseudoprogression と脳放射線壊死との間に明確な線を引くことは難しい．一般には pseudoprogression は脳放射線壊死と比べて，画像上の悪化に比して症状は軽く，かつ治療から発症までの期間が短いことが特徴と理解されている．文献 15 で紹介した症例は治療から画像上の増悪までの期間が短く，PET 上も壊死の診断はできず，symptomatic pseudoprogression と判断した症例である．ベバシズマブの治療効果を考えると，今後再発症例の BNCT 後には本治療を適応すべき症例も増加すると考える．

謝　辞

稿を終えるにあたり，大阪医科大学脳神経外科の黒岩敏彦教授以下諸先生，ことに BNCT をともに推進してきた，川端信司先生，ならびに放射線壊死の治療に当たった古瀬元雅先生に心より謝意を表する．また，BNCT のご指導をいただき，ともに加速器 BNCT の治験を推進している，小野公二先生以下，京都大学原子炉実験所の先生方にも深謝する．

文　献

1) Brandsma D, Stalpers L, Taal W, Sminia P, van den Bent MJ: Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas. *Lancet Oncol* **9**: 453-461, 2008.
2) Carson KA, Grossman SA, Fisher JD, Shaw EG: Prognostic factors for survival in adult patients with recurrent glioma enrolled onto the new approaches to brain tumor therapy CNS consortium phase I and II clinical trials. *J Clin Oncol* **25**: 2601-2606, 2007.
3) Coderre JA, Morris GM: Review: The radiation biology of boron neutron capture therapy. *Radiation Res* **151**: 1-18, 1999.
4) Furuse M, Kawabata S, Kuroiwa T, Miyatake S: Repeated treatments with bevacizumab for recurrent radiation necrosis in patients with malignant brain tumors: a report of 2 cases. *J Neurooncol* **102**: 471-475, 2011.
5) Iuchi T, Hatano K, Narita Y, Kodama T, Yamaki T, Osato K: Hypofractionated high-dose irradiation for the treatment of malignant astrocytomas using simultaneous integrated boost technique by IMRT. *Int J Radiat Oncol Biol Phys* **64**: 1317-1324, 2006.
6) Jaaskelainen J, Haltia M, Servo A: Atypical and anaplastic meningiomas: radiology, surgery, radiotherapy, and outcome. *Surg Neurol* **25**: 233-242, 1986.
7) Kawabata S, Miyatake S, Kajimoto Y, Kuroda Y, Kuroiwa T, Imahori Y, Kirihata M, Sakurai Y, Kobayashi T, Ono K: The successful treatment of glioblastoma patients with modified boron neutron capture therapy. Report of two cases. *J Neurooncol* **65**: 159-165, 2003.
8) Kawabata S, Miyatake S, Kuroiwa T, Yokoyama K, Doi A, Iida K, Miyata S, Nonoguchi N, Michiue H, Takahashi M, Inomata T, Imahori Y, Kirihata M, Sakurai Y, Maruhashi A, Kumada H, Ono K: Boron neutron capture therapy for newly diagnosed glioblastoma. *J Radiat Res (Tokyo)* **50**: 51-60, 2009.
9) Miyashita M, Miyatake S, Imahori Y, Yokoyama K, Kawabata S, Kajimoto Y, Shibata MA, Otsuki Y, Kirihata M, Ono K, Kuroiwa T: Evaluation of fluoride-labeled boronophenylalanine-PET imaging for the study of radiation effects in patients with glioblastomas. *J Neurooncol* **89**: 239-246, 2008.
10) Miyatake S, Kawabata S, Kajimoto Y, Aoki A, Yokoyama K, Yamada M, Kuroiwa T, Tsuji M, Imahori Y, Kirihata M, Sakurai Y, Masunaga S, Nagata K, Maruhashi A, Ono K: Modified boron neutron capture therapy for malignant gliomas performed using epithermal neutron and two boron compounds with different accumulation mechanisms: an efficacy study based on findings on neuroimages. *J Neurosurg* **103**: 1000-1009, 2005.
11) Miyatake S, Tamura Y, Kawabata S, Iida K, Kuroiwa T, Ono K: Boron neutron capture therapy for malignant tumors related to meningiomas. *Neurosurgery* **61**: 82-91, 2007.
12) Miyatake S, Kawabata S, Nonoguchi N, Yokoyama K, Kuroiwa T, Matsui H, Ono K: Pseudoprogression in boron neutron capture therapy for malignant gliomas and meningiomas. *Neuro Oncol* **11**: 430-436, 2009.
13) Miyatake S, Kawabata S, Yokoyama K, Kuroiwa T, Michiue H, Sakurai Y, Kumada H, Suzuki M, Maruhashi A, Kirihata M, Ono K: Survival benefit of Boron neutron capture therapy for recurrent malignant gliomas. *J Neurooncol* **91**: 199-206, 2009.
14) 宮武伸一，古瀬元雅：脳放射線壊死の成因と治療—高度医療（第 3 項先進医療）の申請—．脳外誌　**21**：472-479, 2012.
15) Miyatake S, Furuse M, Kawabata S, Maruyama T, Kumabe T, Kuroiwa T, Ono K: Bevacizumab treatment of symptomatic pseudoprogression after boron neutron capture therapy for recurrent malignant gliomas. Report of 2 cases. *Neuro Oncol* **15**: 650-655, 2013.
16) Nonoguchi N, Miyatake SI, Fukumoto M, Furuse M, Hiramatsu R, Kawabata S, Kuroiwa T, Tsuji M, Fukumoto M, Ono K: The distribution of vascular endothelial growth factor-producing cells in clinical radiation necrosis of the brain: pathological consideration of their potential roles. *J Neurooncol* **105**: 423-431, 2011.
17) Ohguri T, Imada H, Kohshi K, Kakeda S, Ohnari N, Morioka T, Nakano K, Konda N, Korogi Y: Effect of prophylactic hyperbaric oxygen treatment for radiation-induced brain injury after stereotactic radiosurgery of brain metastases. *Int J Radiat Oncol Biol Phys* **67**: 248-255, 2007.
18) Palma L, Celli P, Franco C, Cervoni L, Cantore G: Long-term prognosis for atypical and malignant meningiomas: a study of 71 surgical cases. *J Neurosurg* **86**: 793-800, 1997.

19) Tamura Y, Miyatake S, Nonoguchi N, Miyata S, Yokoyama K, Doi A, Kuroiwa T, Asada M, Tanabe H, Ono K: Boron neutron capture therapy for recurrent malignant meningioma. Case report. *J Neurosurg* 105: 898-903, 2006.

20) Tanaka M, Ino Y, Nakagawa K, Tago M, Todo T: High-dose conformal radiotherapy for supratentorial malignant glioma: a historical comparison. *Lancet Oncol* 6: 953-960, 2005.

要　旨

腫瘍細胞選択的粒子線治療「ホウ素中性子捕捉療法」と
抗血管新生薬による症候性脳放射線壊死の治療

宮武　伸一

悪性腫瘍に対する新規放射線（粒子線）治療法として，ホウ素中性子捕捉療法（boron neutron capture therapy：BNCT）が提唱されている．われわれは2002年より本治療法をのべ133例に及ぶ悪性神経膠腫と悪性髄膜腫に適応してきた．また最近，症候性脳放射線壊死に対する抗血管新生療法を積極的に展開している．本論文では，第32回日本脳神経外科コングレス総会「グリオーマ 新しい時代の到来」において発表した上記内容に若干の加筆を行い，ここに発表した．

脳外誌　22：605-612，2013

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RADIATION ONCOLOGY

RESEARCH Open Access

Identification of early and distinct glioblastoma response patterns treated by boron neutron capture therapy not predicted by standard radiographic assessment using functional diffusion map

Ryo Hiramatsu, Shinji Kawabata*, Motomasa Furuse, Shin-Ichi Miyatake and Toshihiko Kuroiwa

Abstract

Background: Radiologic response of brain tumors is traditionally assessed according to the Macdonald criteria 10 weeks from the start of therapy. Because glioblastoma (GB) responds in days rather than weeks after boron neutron capture therapy (BNCT) that is a form of tumor-selective particle radiation, it is inconvenient to use the Macdonald criteria to assess the therapeutic efficacy of BNCT by gadolinium-magnetic resonance imaging (Gd-MRI). Our study assessed the utility of functional diffusion map (fDM) for evaluating response patterns in GB treated by BNCT.

Methods: The fDM is an image assessment using time-dependent changes of apparent diffusion coefficient (ADC) in tumors on a voxel-by-voxel approach. Other than time-dependent changes of ADC, fDM can automatically assess minimum/maximum ADC, Response Evaluation Criteria In Solid Tumors (RECIST), and the volume of enhanced lesions on Gd-MRI over time. We assessed 17 GB patients treated by BNCT using fDM. Additionally, in order to verify our results, we performed a histopathological examination using F98 rat glioma models.

Results: Only the volume of tumor with decreased ADC by fDM at 2 days after BNCT was a good predictor for GB patients treated by BNCT (P value = 0.022 by log-rank test and 0.033 by wilcoxon test). In a histopathological examination, brain sections of F98 rat glioma models treated by BNCT showed cell swelling of both the nuclei and the cytoplasm compared with untreated rat glioma models.

Conclusions: The fDM could identify response patterns in BNCT-treated GB earlier than a standard radiographic assessment. Early detection of treatment failure can allow a change or supplementation before tumor progression and might lead to an improvement of GB patients' prognosis.

Keywords: ADC, BNCT, Diffusion MRI, fDM, GB

Background

Surgery followed by radiation therapy is still the standard treatment for glioblastoma (GB). The addition of temozolomide (TMZ) chemotherapy to the standard treatment has significantly increased the proportion of patients who survive longer than 2 years [1]. However, additional progress is needed, as almost half of GB patients do not survive the first year after diagnosis.

Boron neutron capture therapy (BNCT) has been developed in the hope of achieving a breakthrough in GB treatment [2,3]. BNCT is a form of tumor-selective particle radiation therapy. We have applied BNCT to over 80 GB patients and have reported its survival benefit [4]. Additionally, a phase II multicenter clinical trial of BNCT is currently underway in Japan. In our substantial experience of clinical BNCT, we have frequently experienced dramatic reductions in enhanced lesion size on gadolinium-magnetic resonance imaging (Gd-MRI) obtained 2 to 7 days after BNCT [2,3]. Assessment of

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radiation and chemotherapy efficacy for GB patients is traditionally accomplished by measuring changes in contrast enhancement of tumors at 10 weeks from the start of therapy using Gd-MRI, using the so-called Macdonald criteria [5]. The Macdonald criteria guide standard radiographic assessments, and have been correlated with survival [5-7]. However, because GB responds in days rather than weeks after BNCT, it is inconvenient to use the Macdonald criteria (including the conventional timing) to assess the therapeutic efficacy of BNCT by Gd-MRI.

On the other hand, the current standard treatment for GB patients, combined chemo-irradiation with TMZ, may induce pseudoprogression in 20–30% of cases [8], defined as an increase of contrast enhancement and/or edema on MRI without true tumor progression [9]. Also, full-blown radiation necrosis may be more frequent after combined chemo-irradiation. Pseudoresponse - namely, a decrease in contrast enhancement of brain tumors on MRI without a decrease of tumor activity - is frequent after treatment with vascular endothelial growth factor receptor signalling pathway inhibitors. Just as it is difficult to evaluate response patterns of GB treated by BNCT, so also cases with pseudoprogression, radiation necrosis, or pseudoresponse are difficult to assess using standard radiography because of changes in contrast enhancement that do not reflect tumor activity.

Diffusion MRI, which measures the random (Brownian) motion of water, has been proposed as an early biomarker for tumor response that does not rely on the measurement of contrast enhancement [10], and has been evaluated in preclinical [11,12] and clinical studies [13-15]. Diffusion MRI measurements are sensitive and can be used to detect and quantify tissue water diffusion values, which have been proposed to be related to the ratio of intracellular water to extracellular water; thus, changes in apparent diffusion coefficient (ADC) are inversely correlated with changes in cellularity. In this scenario, increases in ADC would reflect an increase in the mobility of water, either through the loss of membrane integrity or an increase in the proportion of total extracellular fluid with a corresponding decrease in cellular size or number, as seen with necrosis or apoptosis. In contrast, decreases in ADC reflect a decrease in free extracellular water, either through an increase in total cellular size or number, as can be seen with tumor progression or tumor cell swelling [16].

Functional diffusion map (fDM) was developed to take advantage of these principles on a voxel-by-voxel approach, and have proven to be a powerful tool for predicting the effect of chemotherapy and radiotherapy [10,15,17]. An increased ADC has been shown to correlate with a decrease in cellularity as a result of successful treatment [11,18] and/or radiation necrosis [18]. Other than time-dependent changes of ADC, fDM could automatically assess minimum (Min)/maximum (Max) ADC, Response Evaluation Criteria In Solid Tumors (RECIST), and the volume of enhanced lesions in response to BNCT over time.

In the current study, the usefulness of fDM as a predictive biomarker for GB patients treated with radiochemotherapy was reported [14,15]. There are no reports about the usefulness of fDM for GB treated by BNCT. In order to verify the usefulness of fDM for GB patients treated by BNCT, we assessed 17 GB patients treated by BNCT with fDM at 2 days after BNCT and examined a relationship between all the above factors analyzed by fDM (time-dependent changes of ADC, Min/Max ADC, RECIST, and the volume of enhanced lesions) and prognosis of GB patients treated by BNCT. Additionally, we treated F98 rat glioma models with BNCT and compared brain sections of the BNCT group with the untreated group using hematoxylin-eosin (H & E) staining.

Methods

Patient population

We performed a retrospective investigation of clinical BNCT to evaluate the effects of therapy and adverse events. From June 2003 to December 2007, we treated a total of 61 GB patients using BNCT. Because 17 of these 61 GB patients (8 females; 9 males) had diffusion MRI at pre- and post-BNCT and had contrast enhancement volumes over 0.7 cm^3 on Gd-MRI, we were able to assess them using fDM. Ten patients were newly diagnosed with GB and 7 patients were recurrent GB cases. The average age was 56.7 years (36–74 years). The average survival time from BNCT was 14.5 months (7.2 - 45.9 months). The average volume of contrast enhancement on Gd-MRIs was 18.8 cm^3 (0.7 - 51.4 cm^3).

Our treatment for GB patients and boron neutron capture therapy protocol

Our treatment for GB patients was surgical resection as much of the tumor as possible, followed by BNCT. Our BNCT protocol was as follows:

Twelve hours before the neutron irradiation, the patients were administered 100 mg/kg or none of sodium borocaptate intravenously for 1 hour. Boronophenylalanine (BPA) of 250 mg/kg was infused continuously to the patients for 1 hours or 700 mg/kg was infused continuously to the patients for 6 hours before the irradiation, and they were positioned for neutron irradiation in the atomic reactor (Kyoto University Research Reactor [KUR] or Japan Atomic Energy Agency Research Reactor 4). Just after termination of continuous BPA infusion for 6 hours, neutrons were irradiated. Between June 2003 and December 2006, no chemotherapy was applied for any of the patients until the tumor progression was confirmed histologically or by

^{18}F-BPA-positron emission tomography [19]. This protocol was approved by the Ethical Committee of Osaka Medical College and also by the Committee for Reactor Medicine in KUR. The indication of BNCT for each candidate was discussed by the latter committee.

MRI examinations

All patients underwent pre-BNCT MRI within 20 days before BNCT and underwent post-BNCT MRI at 2 days after BNCT. MRI examinations were composed of T1-weighted images MRI, T2-weighted images, fluid attenuation inversion recovery (FLAIR) images, Gd-T1-weighted images and diffusion images. MRI was performed on a 1.5-T MRI system (GE; Wisconsin, Milwaukee, USA). MRI sequences included T1-weighted images (TE/TR = 9 ms/2500 ms, slice thickness = 5 mm with 2.5 mm interslice distance, number of excitations [NEX] = 1, matrix size = 256 × 224, and field of view [FOV] = 24 cm), T2-weighted images (TE/TR = 103 ms/2500 ms, slice thickness = 5 mm with 2.5 mm interslice distance, NEX = 1, matrix size = 320 × 192, and FOV = 24 cm), and FLAIR images (inversion time = 2200 ms, TE/TR = 116.7 ms/8800 ms, slice thickness = 5 mm with 2.5 mm interslice distance, NEX = 1, matrix size = 256 × 192, and FOV = 24 cm). In addition, Gd-T1-weighted images (axial: TE/TR = 9 ms/400 ms, slice thickness 5 mm with 2.5 mm interslice distance, NEX = 1, a matrix size of 256 × 224, and FOV = 24 cm) were acquired after contrast injection (Magnevist; Berlex; 0.1 mmol/kg) (Table 1).

Diffusion MRI

Diffusion MRI was collected with TE/TR = 79.3 ms/6400 ms, NEX = 1, slice thickness = 5 mm with 0 mm interslice distance, matrix size = 128 × 192 and a FOV = 24 cm. ADC images were calculated from acquired DWIs with b = 1000 s/mm^2 and b = 0 s/mm^2 images (Table 1). Diffusion images for the three orthogonal directions were combined to calculate an ADC map [20].

Table 1 Summarizing the details of MRI sequences

MRI Sequences	T1	T2	FLAIR	DWI	Gd-T1
TR (ms)	2500	4000	8800	4500	400
TE (ms)	9	103	116.7	67.7	9
inversion time (ms)			2200		
FOV* (cm)	24	24	24	24	24
slice thickness (mm)	5	5	5	5	5
interslice distance (mm)	2.5	2.5	2.5	0	2.5
frequency matrix	256	320	256	128	256
phase matrix	224	192	192	192	224
NEX**	1	1	1	2	1
scan time (s)	107	144	121	64	94

*FOV = field of view **NEX = number of excitations.

fDM analysis

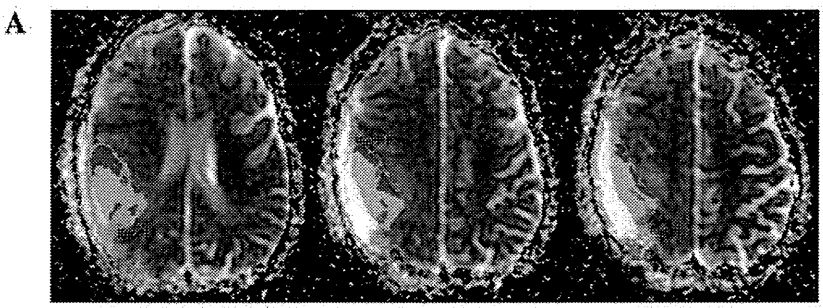
All MRIs were spatially co-registered using the pre-BNCT Gd-MRI as the reference dataset. This step allowed all images of a given patient to be viewed and analyzed from a fixed frame of reference. The co-registration was performed using a "mutual information for automatic multimodality image fusion" (MIAMI FUSE) algorithm [21]. After this co-registration, brain tumors were manually segmented on the Gd-MRIs by a neurosurgeon (R. H.). These segmentations were copied into the contemporary diffusion MRIs and were analyzed using a voxel-by-voxel approach [17,22]. A minimum of 0.7 cm^3 of tumor on Gd-MRI was necessary for eligibility. If a resection cavity was present, it wasn't included within the regions of interest if circumscribed by contrast enhancement. Only voxels present in both the pre-BNCT and post-BNCT tumor volumes were included for fDM analysis. Individual voxels were stratified into three categories based on the change in ADC from the pre-BNCT scan to each time point. Red voxels represent areas within the tumor where ADC increased (> 55 × 10^{-5} mm^2/sec); blue voxels represent decreased ADC (< 55 × 10^{-5} mm^2/sec), and green voxels represent no change (Figure 1). These thresholds represent the 95% confidence intervals for change in ADC for the uninvolved cerebral hemisphere [17]. The percentages of the tumor within these three categories were calculated as V_I, V_D, and V_{NC}, respectively. Other than time-dependent changes of ADC, fDM could automatically assess Min/Max ADC, RECIST, and the volume of enhanced lesions in response to BNCT over time. These analyses were performed using fDM analysis software (*I-Response™-1.0*, Cedara software; Ontario Canada).

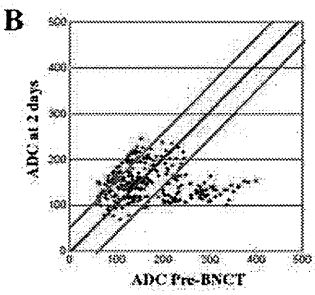
Representative case

This patient was newly diagnosed GB with 23.2 months of patients' survival time after BNCT. Depicted images are single slices of Gd-MRI scans at 2 days after BNCT with a pseudocolor overlay of the fDM. Red voxels indicate regions with a significant rise in ADC at 2 days after BNCT compared with pre-BNCT, green regions had no changed ADC, and blue voxels indicate areas of significant decline in ADC (Figure 1A). The scatter plots display data for the entire tumor volume and not just for the depicted slice at 2 days after BNCT, with ADC of the pre-BNCT on the x-axis and ADC at 2 days after BNCT on the y-axis. The central red line represents unity, and the flanking blue lines represent the 95% confidence interval (CI) (Figure 1B). Other than time-dependent changes of ADC, fDM can automatically assess maximum/minimum ADC, RECIST, and the volume of enhanced lesions on Gd-MRI over time (Figure 1C).

Correlation with all factors assessed by fDM and survival time after BNCT

All factors assessed by fDM are composed of V_I, V_D, V_{NC}, Min/Max ADC, RECIST, and the volume reduction





C

All factors assessed by fDM at 2 days after BNCT

V_D (%)	V_I (%)	V_{NC} (%)	V_D+V_I+V_{NC} (%)	Min ADC (10^{-5} mm^2/sec)	Max ADC (10^{-5} mm^2/sec)	RECIST (cm)	Volume Reduction Rate (%)
26.8	16.7	56.5	100	55.0	251.0	26.3	29.8

Figure 1 Representative case: Regions of interests were drawn for tumor image by using anatomical images (A). Red voxels represent areas within the tumor where ADC increased (> 55 × 10^{-5} mm^2/sec); blue voxels represent decreased ADC (< 55 × 10^{-5} mm^2/sec), and green voxels represent no change. These thresholds represent the 95% confidence intervals for change in ADC for the uninvolved cerebral hemisphere **(B)**. V_D, V_I, V_{NC}, Min/Max ADC, RECIST, and the volume of enhanced lesions on Gd-MRI over time showed 26.8%, 16.7%, 56.5%, 55.0 10^{-5} mm^2/sec, 251.0 10^{-5} mm^2/sec, 26.3 cm, and 29.8% at 2 days after BNCT, respectively **(C)**.

rate of enhanced lesions. The end point in this study was a survival time after BNCT. Survival analysis utilized log-rank and wilcoxon test. Statistical analysis utilized JMP® Pro 10 (SAS Institute Inc., Cary, NC, USA).

Tumor models

F98 rat glioma cells produce infiltrating tumors in the brains of Fischer rats [23]. The tumors have been shown to be refractory to a number of treatment modalities, including radiation therapy [24]. Based on their *in vivo* histology, the F98 rat glioma cells have been characterized as anaplastic or undifferentiated glioma [25]. In the present study, F98 rat glioma cells were kindly obtained from Prof. Barth (Department of Pathology, the Ohio State University, Columbus, OH, USA). They were routinely cultivated in our laboratory in Dulbecco's Modified Eagle Medium supplemented with 10% fetal bovine serum and penicillin at 37°C in an atmosphere of 5% CO_2. All the materials for the culture medium were purchased from Gibco Invitrogen (Grand Island, NY, USA). Male Fischer rats weighing 200–250 g were anesthetized with an intraperitoneal injection of Nembutal (50 mg/kg) and placed in a stereotactic frame (Model 900, David Kopf Instruments, Tujunga, CA, USA). A midline scalp incision was made and the bregma was identified. A 1mm burr hole was made in the right frontal region of the skull and a 22-gauge needle attached to a 25-μl syringe was inserted into the caudate nucleus using the same stereotactic coordinates, with the needle tip inserted 5 mm into the dura. An injection of 10^3 F98 rat glioma cells in 10 μl of serum free medium was administered at a rate of 1 μl/min. After the infusion, the needle was left in place for 3 min and the burr hole was then covered with bone wax.

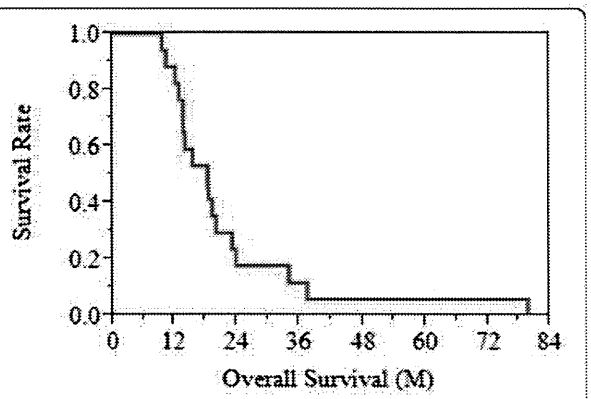


Figure 2 Overall survival of all patients: Median overall survival was 18.5 months (95% CI; 12.9 - 23.2 months).

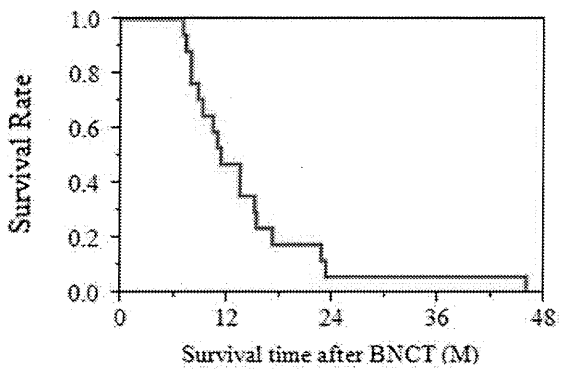


Figure 3 Survival time after BNCT of all patients: Median survival time after BNCT was 11.2 months (95% CI; 7.8 - 15.3 months).

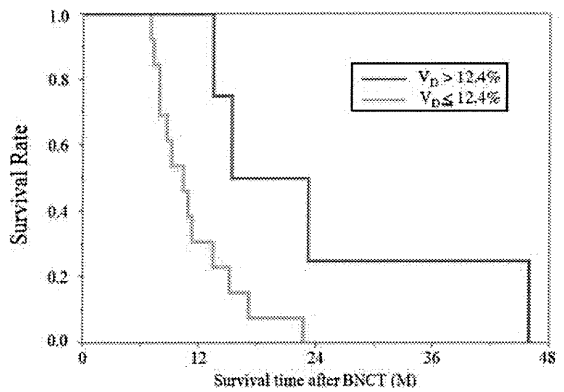


Figure 4 Survival analysis of V_D at 2 days after BNCT: V_D greater than 12.4% at 2 days after BNCT was good response for BNCT (median survival = 19.3 months; 95% CI = 13.4 - 45.9 months) and V_D 12.4% or less at 2 days after BNCT was nonresponse for BNCT (median survival = 10.3 months; 95% CI = 7.8 - 13.4 months).

Histopathological examination

At 2 weeks after implantation, the BNCT group was administered 250 mg/kg body weight of BPA intravenously. An hour and a half after BPA injection, only the BNCT group was irradiated with neutrons at KUR during 1 hour. All rats of both the BNCT group and the untreated group were euthanized by isoflurane 16 days after implantation (i.e., 2 days after BNCT for the BNCT group). The rats were perfused and fixed by 10% formalin; then the brains were dehydrated and embedded in paraffin. The 4-μm sections were stained with hematoxylin and eosin (H & E) for histopathological investigation. We compared sections of the BNCT group with the untreated group using a light microscope (ECLIPSE80i, Nikon, Japan).

Results

MRI examination

In our study, pre-BNCT MRI was performed at 7.9 ± 5.0 (1–20) days before BNCT, and post-BNCT MRI was performed at 2.5 ± 1.6 (1–8) days after BNCT.

Overall survival and survival time after BNCT of all patients

Median overall survival was 18.5 months (95% CI; 12.9 - 23.2 months) (Figure 2) and median survival time after BNCT was 11.2 months (95% CI; 7.8 - 15.3 months) (Figure 3).

Correlation with all factors assessed by fDM and survival time after BNCT

V_D and Min ADC at 2 days after BNCT showed a significant difference using log-rank test and wilcoxon test. However, Min ADC showed over-lap in 95% CI. On the other hand, V_D showed no over-lap in 95% CI (Table 2). V_D greater than 12.4% at 2 days after BNCT was good response for BNCT (median survival = 23.2 months; 95% CI = 13.4 - 45.9 months) and V_D 12.4% or less at 2 days after BNCT was nonresponse for BNCT (median survival = 10.3 months; 95% CI = 7.8 - 13.4 months) (Figure 4). Survival analysis of V_D showed a significant difference (P value = 0.022 by log-rank test and 0.033 by

Table 2 Survival analysis of all factors assessed by fDM

	All factors assessed by fDM													
	V_D (%)		V_I (%)		V_{NC} (%)		Min ADC (10^{-5} mm2/sec)		Max ADC (10^{-5} mm2/sec)		RECIST (cm)		Volume reduction rate of enhanced lesion (%)	
	> 12.4	≤ 12.4	< 3.6	≥ 3.6	< 74.6	≥ 74.6	< 70	≥ 70	< 368	≥ 368	< 40.3	≥ 40.3	< −21.1	≥ −21.1
Median time (M)	19.3	10.3	11.2	12.1	15.3	11	14.3	9.1	11.2	12.1	14.2	10.8	15.1	9.7
95% CI	13.4-	7.8-	7.2-	7.8-	6.9-	7.8-	7.8-	7.2-	7.2-	6.9-	7.8-	7.2-	11.2-	7.2-
(M)	45.9**	13.4**	45.9	15.3	45.9	15.1	22.7**	10.8**	23.2	15.1	45.9	15.1	45.9	15.3
p value log-rank	0.022*		0.521		0.128		0.011*		0.176		0.118		0.143	
wilcoxon	0.033*		0.834		0.35		0.045*		0.413		0.223		0.083	

*V_D and Min ADC at 2 days after BNCT showed a significant difference using log-rank test and wilcoxon test. **However, Min ADC showed over-lap in 95% CI. On the other hand, V_D showed no over-lap in 95% CI.

wilcoxon test). However, V_I, V_{NC}, Max ADC, RECIST, and the volume reduction rate of enhanced lesions at 2 days after BNCT had no correlation with patients' survival time after BNCT (Figure 5, Table 2).

Histopathological examination

Tumor cells in the BNCT group showed swelling of both the nuclei and the cytoplasm compared with the untreated group at 16 days after implantation (i.e., 2 days after BNCT for the BNCT group) (Figure 6).

Discussion

In 1990, Macdonald *et al.* reported criteria for response assessment in glioma [5]. Although these criteria have limitations, they have become widely accepted. However, recent observations have revealed the fundamental limitations of the Macdonald criteria [26,27]. One limitation of the Macdonald criteria is the extended time required to detect change [5,28,29], about 8 to 10 weeks. Another is the discrepancy between contrast enhancement and tumor activity. At the core of Macdonald criteria are changes in contrast enhancement, and all too often, the contrast enhancement of high-grade tumors is perceived as a measure of tumor activity. However, contrast enhancement is nonspecific and primarily reflects a disrupted blood–brain barrier. Contrast enhancement can be influenced by changes in corticosteroid dose and radiologic technique [9,30]. Contrast enhancement can also be induced by a variety of nontumoral processes: inflammation, seizure activity, postsurgical changes, pseudoprogression, radiation necrosis,

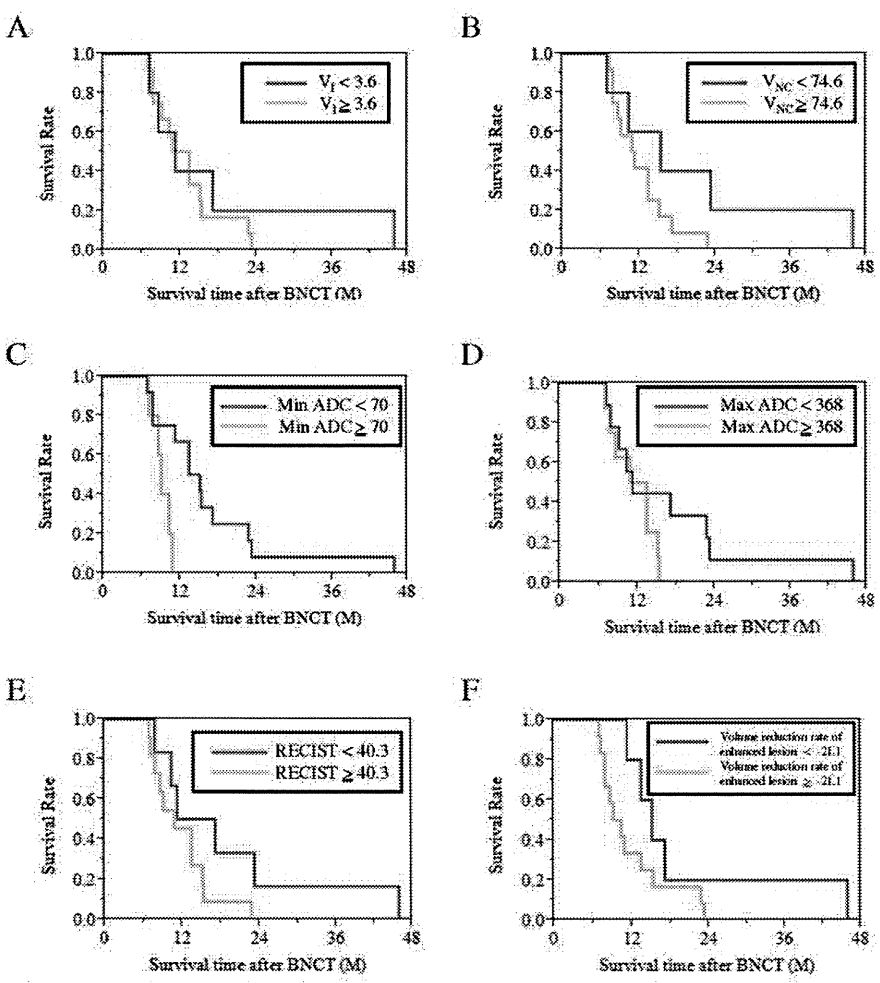


Figure 5 Survival analysis except for V_D at 2 days after BNCT: V_I, V_{NC}, Max ADC, RECIST, and the volume reduction rate of enhanced lesions at 2 days after BNCT (A, B, D, E, and F, respectively) had no correlation with patients' survival time after BNCT using log-rank test and wilcoxon test. Min ADC at 2 days after BNCT **(C)** showed a significant difference using log-rank test and wilcoxon test. However, Min ADC showed over-lap in 95% CI (Table 2).

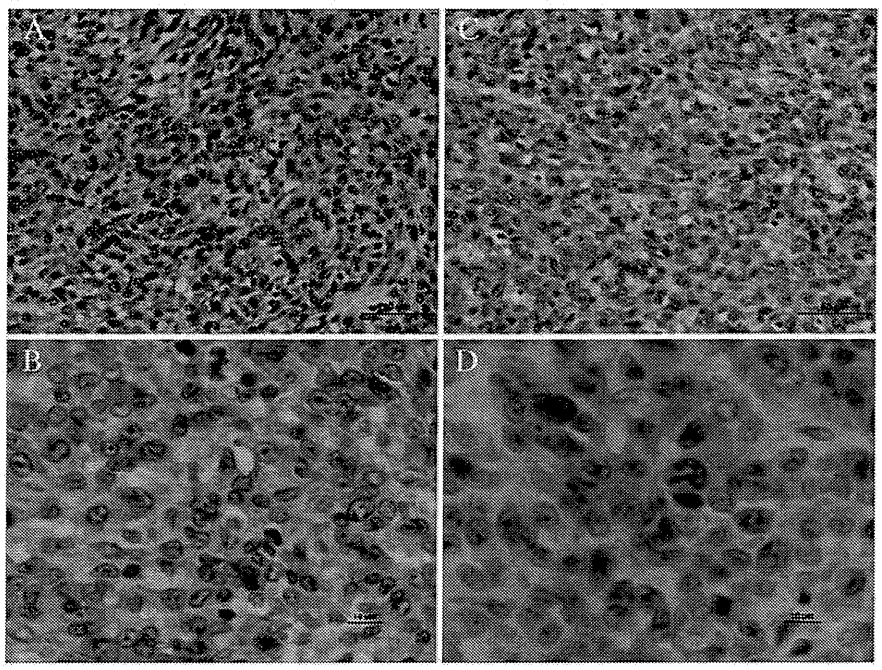


Figure 6 Histopathological examination: Tumor cells in the BNCT group showed the cell swelling of both the nuclei and the cytoplasm (C and D) compared with the untreated group (A and B) at 16 days after the implantation (i.e., at 2 days after BNCT for the BNCT group). (A and C were at 400-fold. B and D were 1000-fold magnification).

and pseudoresponse [9,31]. As a result, changes in contrast enhancement cannot be equated with changes in tumor size or tumor growth/activity.

Recently, several novel imaging methods—positron-emission tomography, single-photon emission computerized tomography, MR spectroscopy, and diffusion MRI—have been evaluated for their ability to assess early therapeutic responses independently of late changes in enhanced tumor volume [32,33]. Diffusion MRI detection of cancer treatment response was first successfully reported in a rodent brain tumor model treated with chemotherapy. Additionally, Diffusion MRI has been evaluated in preclinical [11,12,34] and clinical studies [13,34,35]. In 2008, Hamstra *et al.* assessed high-grade glioma with functional diffusion map. They reported that the volume of tumor with increased diffusion by fDM at 3 weeks after the start of radiation therapy was the strongest predictor of patient survival at 1 year [10].

In our study, V_D at 2 days after BNCT was the strongest predictor of GB patients' survival time after BNCT. V_D (= the volume of the voxels with decreased ADC compared with pre-BNCT by fDM) indicates that extracellular free water is relatively decreased for the highest volume of tumor cells. So, this appearance is attributed to tumor progression or tumor cell swelling as previously mentioned in the ***Background***. In our study, day 2 V_D was a good predictor for GB patients treated by BNCT. We attributed this higher V_D to tumor cell swelling rather than tumor progression. In fact, our histopathological study detected tumor cell swelling in the BNCT group compared with the untreated group at 16 days after the implantation (i.e., at 2 days after BNCT for the BNCT group) (Figures 5 and 6). Others have reported tumor cell swelling in the acute stage after BNCT. Kato *et al.* reported the pathological changes of oral squamous cell carcinoma at an early stage after BNCT using nude mouse subcutaneous models. They compared a BNCT group with an untreated group using pathological analysis at 1, 2, and 7 days after BNCT. Compared to the untreated group, oral squamous cell carcinoma in the BNCT group at all early stages showed tumor cell swelling on the H & E stained nude mouse brain sections [36]. Nakagawa *et al.* reported early effects of BNCT on C6 rat glioma models. They compared a BNCT group with an untreated group using pathological analysis at 4days after BNCT. Compared to the untreated group, C6 rat glioma cell in the BNCT group showed cell swelling on the H & E stained rat brain sections [37].

Conclusions

Our study proved that fDM was useful for evaluating the therapeutic efficacy of BNCT in GB patients treated by BNCT. Additionally, fDM could identify response patterns in BNCT-treated GB earlier than a standard radiographic assessment. Early detection of treatment failure can allow a change or supplementation before tumor progression and might lead to an improvement of GB patients' prognosis.

Abbreviations

ADC: Apparent diffusion coefficient; BNCT: Boron neutron capture therapy; BPA: Boronophenylalanine; CI: Confidence interval; fDM: functional diffusion map; FLAIR: Fluid attenuation inversion recovery; FOV: Field of view; GB: Glioblastoma; Gd: Gadolinium; H & E: Hematoxylin and Eosin; KUR: Kyoto university research reactor; Max: Maximum; Min: Minimum; MRI: Magnetic resonance imaging; NEX: Number of excitations; RECIST: Response evaluation criteria in solid tumors; TMZ: Temozolomide.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

RH carried out all the animal study and the statical analysis, and drafted the manuscript. SK conceived of the study, and participated in its design and coordination and helped to draft the manuscript. MF, S-IM, and TK participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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References

1. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, *et al*: **Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma.** *N Engl J Med* 2005, **352**:987–996.
2. Kawabata S, Miyatake S, Nonoguchi N, Hiramatsu R, Iida K, Miyata S, Yokoyama K, Doi A, Kuroda Y, Kuroiwa T, *et al*: **Survival benefit from boron neutron capture therapy for the newly diagnosed glioblastoma patients.** *Appl Radiat Isot* 2009, **67**:S15–18.
3. Miyatake S, Kawabata S, Kajimoto Y, Aoki A, Yokoyama K, Yamada M, Kuroiwa T, Tsuji M, Imahori Y, Kirihata M, *et al*: **Modified boron neutron capture therapy for malignant gliomas performed using epithermal neutron and two boron compounds with different accumulation mechanisms: an efficacy study based on findings on neuroimages.** *J Neurosurg* 2005, **103**:1000–1009.
4. Kawabata S, Miyatake S, Kuroiwa T, Yokoyama K, Doi A, Iida K, Miyata S, Nonoguchi N, Michiue H, Takahashi M, *et al*: **Boron neutron capture therapy for newly diagnosed glioblastoma.** *J Radiat Res* 2009, **50**:51–60.
5. Macdonald DR, Cascino TL, Schold SC Jr, Cairncross JG: **Response criteria for phase II studies of supratentorial malignant glioma.** *J Clin Oncol* 1990, **8**:1277–1280.
6. Wood JR, Green SB, Shapiro WR: **The prognostic importance of tumor size in malignant gliomas: a computed tomographic scan study by the Brain Tumor Cooperative Group.** *J Clin Oncol* 1988, **6**:338–343.
7. Hess KR, Wong ET, Jaeckle KA, Kyritsis AP, Levin VA, Prados MD, Yung WK: **Response and progression in recurrent malignant glioma.** *Neuro Oncol* 1999, **1**:282–288.
8. Taal W, Brandsma D, De Bruin HG, Bromberg JE, Swaak-Kragten AT, Smitt PA, van Es CA, van den Bent MJ: **Incidence of early pseudo-progression in a cohort of malignant glioma patients treated with chemoirradiation with temozolomide.** *Cancer* 2008, **113**:405–410.
9. Brandsma D, van den Bent MJ: **Pseudoprogression and pseudoresponse in the treatment of gliomas.** *Curr Opin Neurol* 2009, **22**:633–638.
10. Hamstra DA, Galban CJ, Meyer CR, Johnson TD, Sundgren PC, Tsien C, Lawrence TS, Junck L, Ross DJ, Rehemtulla A, *et al*: **Functional diffusion map as an early imaging biomarker for high-grade glioma: correlation with conventional radiologic response and overall survival.** *J Clin Oncol* 2008, **26**:3387–3394.
11. Chenevert TL, McKeever PE, Ross BD: **Monitoring early response of experimental brain tumors to therapy using diffusion magnetic resonance imaging.** *Clin Cancer Res* 1997, **3**:1457–1466.
12. Poptani H, Puumalainen AM, Grohn OH, Loimas S, Kainulainen R, Yla-Herttuala S, Kauppinen RA: **Monitoring thymidine kinase and ganciclovir-induced changes in rat malignant glioma in vivo by nuclear magnetic resonance imaging.** *Cancer Gene Ther* 1998, **5**:101–109.
13. Mardor Y, Roth Y, Lidar Z, Jonas T, Pfeffer R, Maier SE, Faibel M, Nass D, Hadani M, Orenstein A, *et al*: **Monitoring response to convection-enhanced taxol delivery in brain tumor patients using diffusion-weighted magnetic resonance imaging.** *Cancer Res* 2001, **61**:4971–4973.
14. Ellingson BM, Cloughesy TF, Lai A, Nghiemphu PL, Liau LM, Pope WB: **Quantitative probabilistic functional diffusion mapping in newly diagnosed glioblastoma treated with radiochemotherapy.** *Neuro Oncol* 2013, **15**:382–390.
15. Ellingson BM, Cloughesy TF, Zaw T, Lai A, Nghiemphu PL, Harris R, Lalezari S, Wagle N, Naeini KM, Carrillo J, *et al*: **Functional diffusion maps (fDMs) evaluated before and after radiochemotherapy predict progression-free and overall survival in newly diagnosed glioblastoma.** *Neuro Oncol* 2012, **14**:333–343.
16. Armitage PA, Schwindack C, Bastin ME, Whittle IR: **Quantitative assessment of intracranial tumor response to dexamethasone using diffusion, perfusion and permeability magnetic resonance imaging.** *Magn Reson Imaging* 2007, **25**:303–310.
17. Hamstra DA, Chenevert TL, Moffat BA, Johnson TD, Meyer CR, Mukherji SK, Quint DJ, Gebarski SS, Fan X, Tsien CI, *et al*: **Evaluation of the functional diffusion map as an early biomarker of time-to-progression and overall survival in high-grade glioma.** *Proc Natl Acad Sci U S A* 2005, **102**:16759–16764.
18. Lyng H, Haraldseth O, Rofstad EK: **Measurement of cell density and necrotic fraction in human melanoma xenografts by diffusion weighted magnetic resonance imaging.** *Magn Reson Med* 2000, **43**:828–836.
19. Miyashita M, Miyatake S, Imahori Y, Yokoyama K, Kawabata S, Kajimoto Y, Shibata MA, Otsuki Y, Kirihata M, Ono K, Kuroiwa T: **Evaluation of fluoride-labeled boronophenylalanine-PET imaging for the study of radiation effects in patients with glioblastomas.** *J Neurooncol* 2008, **89**:239–246.
20. Le Bihan D, Breton E, Lallemand D, Aubin ML, Vignaud J, Laval-Jeantet M: **Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging.** *Radiology* 1988, **168**:497–505.
21. Meyer CR, Boes JL, Kim B, Bland PH, Zasadny KR, Kison PV, Koral K, Frey KA, Wahl RL: **Demonstration of accuracy and clinical versatility of mutual information for automatic multimodality image fusion using affine and thin-plate spline warped geometric deformations.** *Med Image Anal* 1997, **1**:195–206.
22. Moffat BA, Chenevert TL, Meyer CR, McKeever PE, Hall DE, Hoff BA, Johnson TD, Rehemtulla A, Ross BD: **The functional diffusion map: an imaging biomarker for the early prediction of cancer treatment outcome.** *Neoplasia* 2006, **8**:259–267.
23. Barth RF: **Rat brain tumor models in experimental neuro-oncology: the 9L, C6, T9, F98, RG2 (D74), RT-2 and CNS-1 gliomas.** *J Neurooncol* 1998, **36**:91–102.
24. Biston MC, Joubert A, Adam JF, Elleaume H, Bohic S, Charvet AM, Esteve F, Foray N, Balosso J: **Cure of Fisher rats bearing radioresistant F98 glioma treated with cis-platinum and irradiated with monochromatic synchrotron X-rays.** *Cancer Res* 2004, **64**:2317–2323.
25. Kobayashi N, Allen N, Clendenon NR, Ko LW: **An improved rat brain-tumor model.** *J Neurosurg* 1980, **53**:808–815.
26. Henson JW, Ulmer S, Harris GJ: **Brain tumor imaging in clinical trials.** *AJNR Am J Neuroradiol* 2008, **29**:419–424.
27. Sorensen AG, Batchelor TT, Wen PY, Zhang WT, Jain RK: **Response criteria for glioma.** *Nat Clin Pract Oncol* 2008, **5**:634–644.
28. Miller AB, Hoogstraten B, Staquet M, Winkler A: **Reporting results of cancer treatment.** *Cancer* 1981, **47**:207–214.
29. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG: **New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada.** *J Natl Cancer Inst* 2000, **92**:205–216.
30. Watling CJ, Lee DH, Macdonald DR, Cairncross JG: **Corticosteroid-induced magnetic resonance imaging changes in patients with recurrent malignant glioma.** *J Clin Oncol* 1994, **12**:1886–1889.

31. Kumar AJ, Leeds NE, Fuller GN, Van Tassel P, Maor MH, Sawaya RE, Levin VA: **Malignant gliomas: MR imaging spectrum of radiation therapy- and chemotherapy-induced necrosis of the brain after treatment.** *Radiology* 2000, **217**:377–384.
32. Spence AM, Mankoff DA, Muzi M: **Positron emission tomography imaging of brain tumors.** *Neuroimaging Clin N Am* 2003, 13:717–739.
33. Van de Wiele C, Lahorte C, Oyen W, Boerman O, Goethals I, Slegers G, Dierckx RA: **Nuclear medicine imaging to predict response to radiotherapy: a review.** *Int J Radiat Oncol Biol Phys* 2003, **55**:5–15.
34. Chenevert TL, Stegman LD, Taylor JM, Robertson PL, Greenberg HS, Rehemtulla A, Ross BD: **Diffusion magnetic resonance imaging: an early surrogate marker of therapeutic efficacy in brain tumors.** *J Natl Cancer Inst* 2000, **92**:2029–2036.
35. Mardor Y, Pfeffer R, Spiegelmann R, Roth Y, Maier SE, Nissim O, Berger R, Glicksman A, Baram J, Orenstein A, *et al*: **Early detection of response to radiation therapy in patients with brain malignancies using conventional and high b-value diffusion-weighted magnetic resonance imaging.** *J Clin Oncol* 2003, **21**:1094–1100.
36. Kamida A, Obayashi S, Kato I, Ono K, Suzuki M, Nagata K, Sakurai Y, Yura Y: **Effects of boron neutron capture therapy on human oral squamous cell carcinoma in a nude mouse model.** *Int J Radiat Biol* 2006, **82**:21–29.
37. Nakagawa N, Akai F, Fukawa N, Fujita Y, Suzuki M, Ono K, Taneda M: **Early effects of boron neutron capture therapy on rat glioma models.** *Brain Tumor Pathol* 2007, **24**:7–13.

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