Prognostic factors in the consecutive institutional series of glioblastoma multiforme patients who received high-dose particle radiotherapy or conventional radiotherapy

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short title: prognostic significance of high-dose particle radiotherapy

Abstract

To evaluate the influence of prognostic factors related to patient selection on survival data, survival outcomes were retrospectively analyzed using our institutional consecutive series of 67 newly diagnosed glioblastoma multiforme (GBM) patients who had received either conventional fractionated photon radiotherapy (CRT) or high-dose particle radiotherapy (HDT).

In CRT protocol, a total dose of 60.0-61.2 Gy was administered. In HDT protocol, an averaged dose of approximately 30 GyEq at a single session and additional fractionated photon irradiation at a total dose of 30 Gy was administered in boron neutron capture therapy, and a total dose of 96.6GyEq was administered in proton therapy. Most of the patients had received chemotherapy with nimustine hydrochloride (ACNU) alone or with ACNU, procarbazine, and vincristine. The median overall and progression-free survival time for all patients was 17.7 months (95% CI, 14.6 – 20.9) and 7.8 months (95% CI, 5.7 – 9.9), respectively. The one- and two-year survival rate was 67.2% and 33.7%, respectively. The median overall survival time (OS) was 24.4 months (95% CI, 18.2 – 30.5) for patients treated with HDT, compared with 14.2 months (95% CI, 10.0 – 18.3) for those with CRT. The Cox proportional hazards model revealed radiation modality (HDT vs. CRT) and EORTC-RPA class to be the significant prognostic factors. Age, sex, preoperative performance status, treatment with or without advanced neuro-imaging, extent of surgery, and regimen of chemotherapy were not statistically significant. The median OS was 18.5 months (95% CI, 9.9 – 27.1) in patients 65 years

and older, compared with 16.8 months (95% CI, 13.6 – 20.1) in those 64 years and younger (p=0.871).

The relatively positive survival data of selected patients who underwent HDT are unlikely to reflect patient selection alone. Randomized trials with strictly controlled inclusion criteria for the comparable selection of patients will still be required to demonstrate conclusively that prolonged survival can be attributed to these high-dose particle radiotherapies.

Introduction

Glioblastoma multiforme (GBM) is a highly infiltrative primary malignant brain tumour in adults. The prognosis of GBM is generally extremely poor, and there has been little improvement in survival rates over the past three decades [1, 2]. Several randomized trials have demonstrated the survival benefits of conventional fractionated photon radiotherapy at a total dose of 45 to 60 Gy; the median overall survival time (OS) in these trials was 5.8 to 15.5 months [3–7]. Currently, conventional fractionated photon radiotherapy of approximately 60 Gy with concomitant and adjuvant use of temozolomide has been recognized as the standard postoperative treatment for newly diagnosed GBM [8, 9]. However, the five-year survival rate with this standard therapy is less than 10 % [9], suggesting that alternative therapeutic strategies are desperately needed.

Most dose escalation studies of radiotherapy have been designed as case series of a small number of selected patients who underwent additional stereotactic radiosurgery, fractionated proton beam radiation, or intensity-modulated radiotherapy or another type of conformal radiotherapy [10-12]. Studies showing the better outcomes (median OS range: 9.5 - 25 months) suggested that a radiation dose of at least 90 Gy of hyperfractionated radiotherapy should be used for irradiation in order to accomplish local tumour control. However, there has been no randomized controlled trial (RCT) to provide evidence in support of these favorable data, nor has there been any trial warranting a follow-up study using any form of high-dose radiotherapy [10, 13]. Thus, controversy remains

regarding not only the efficacy of high-dose radiotherapy but also regarding the influence of strict patient selection on outcomes achieved with this type of treatment. High-dose irradiation of a small-volume target could minimize central recurrence and any radiation dose-dependent adverse events in such trials. However, recurrences often occur in the target volume receiving a relatively low-dose treatment. The five-year survival rate with conventional-dose radiotherapy alone is reported around 1% [9], which suggested a limitation of conventional-dose radiotherapy in most patients.

We recently reported two different types of high-dose particle radiotherapy using boron neutron capture therapy (BNCT) and proton therapy (PT). These radiotherapies for newly-diagnosed GBM were administered based on different selection criteria, and both showed an acceptable OS (i.e., 25.7 months in the BNCT group, and 21.6 months in PT group), with acceptable adverse events [14, 15]. Previously, several different factors (e.g., age, preoperative performance status [PS], tumour location, extent of surgery, and conventional radiotherapy) have been shown to be prognostic of survival in patients with GBM [16-20]. Here we aimed to evaluate the influence of such patient selection-related factors on survival. Survival outcomes and prognostic factors were retrospectively analyzed using our institutional consecutive series of newly diagnosed GBM patients who had received either conventional fractionated photon radiotherapy (CRT) or high-dose particle radiotherapy (HDT). In the present paper, we report the combined updated results of all patients treated by both forms of particle therapy.

Materials and Methods

We investigated 67 consecutive patients with newly diagnosed supratentorial GBM (grade IV) who were treated at Tsukuba University Hospital from January 1998 to August 2007. The patients were histopathologically diagnosed according to the classification system of the World Health Organization. Some of the survival data for patients who received PT or BNCT have been reported in earlier publications using different follow-up periods and survival analysis determinations [14, 15].

Maximal safe resection was intended to remove all gadolinium (Gd)-enhanced masses observed by magnetic resonance (MR) imaging, i.e., the surrounding non-eloquent brain tissue was targeted for removal, with the aim of preserving neurological function in unresected areas of eloquent brain tissue. To this end, 5-aminolevulinic-acid-induced fluorescence guidance, neuronavigation, as well as intraoperative monitoring were incorporated into the treatment. The navigation-guided fence-post procedure was carried out as previously reported [21] in order to treat non-eloquent portions of tumours. In cases involving tumours located close to areas of eloquent tissue, we inserted silicon tubes along the boundary between the eloquent and non-eloquent tissue, as indicated by MR images. The phrase "advanced neuro-imaging" was used to refer to all surgical interventions involving fluorescence guidance and/or neuronavigation.

The postoperative radiation schedule for patients with GBM treated at our facilities consisted of 3 protocols. As the standard radiotherapy, daily CRT (1.8 - 2.0 Gy) was administered five times per week, amounting to a total overall dose of 60.0 – 61.2 Gy. For selected patients, HDT was used, consisting of either BNCT or PT. In the BNCT protocol, the gross tumor volume (GTV) and clinical target volume (CTV)-1 were defined as the residual gadolinium-enhancing volume. CTV-2 and CTV-3 were defined as GTV plus a margin of 2 cm and 3 cm, respectively. An averaged dose of approximately 30 GyEq at a single session, and additional fractionated photon irradiation at a total dose of 30 Gy was administered to GTV. The detailed protocol of BNCT has been described elsewhere [14]. BNCT was administered to patients with a supratentorial unilateral tumour located at no deeper than 7 cm from the brain surface, and who had a Karnofsky performance status (KPS) of 50 or more. In the PT protocol, CTV-1 was defined same as BNCT. On the other hand, CTV-2 was defined as GTV plus a margin of 1 cm and CTV-3 was defined as the surrounding edema. Furthermore, in the PT protocol, the planning target volume (PTV) was adopted that was defined as the CTV plus a margin of 5 mm for setup error. Conventional photon radiotherapy (50.4 Gy in 28 fractions) was delivered to PTV-3 in the morning. In the first half of the protocol, additional concomitant boost proton radiotherapy (23.1 GyE in 14 fractions) was delivered to PTV-2 more than 6 hours after photon radiotherapy. Then, in the latter half, proton radiotherapy (23.1 GyE in 14 fractions) was delivered to PTV-1. As a result, the total dose for PTV-1 was 96.6 GyE in 56 fractions,

73.5 GyE in 42 fractions for PTV-2, and 50.4 Gy in 28 fractions for PTV-3 [15]. The following criteria were used to select patients for PT: the presence of a supratentorial tumour lacking involvement of the brain stem or thalamus, a maximum postoperative tumour diameter of less than 4 cm, and a KPS of 60 or more. BNCT was administered to 15 patients and PT to 17 patients. The PAV combination regimen of procarbazine, nimustine hydrochloride (ACNU), and vincristine was administered as the standard concomitant chemotherapy combined with CRT. For patients at high risk for adverse events with PAV therapy (i.e., elderly patients, patients in poor neurological or general condition), ACNU alone was typically used as the concomitant chemotherapy. ACNU was also used in combination with HDT.

Statistical analysis

Statistical analyses were performed using SPSS software (version 11.0.1J; SPSS, Inc.). Overall survival and progression-free survival were used to investigate the prognostic impact of the variables analyzed. OS was defined as the time lapse from surgery until death or the final follow-up. Progression-free survival time was defined as the time lapse from surgery until a detection of progression or the final follow-up. Survival probabilities were calculated using the Kaplan-Meier method, and differences among patient groups were evaluated using the log-rank test. The Cox proportional hazards model was used to test the following prognostic factors in univariate and

multivariate analyses: age (<65 years vs. ≥65 years), sex (female vs. male), preoperative PS (0-2 vs. 3-4), European Organization for Research and Treatment of Cancer (EORTC) recursive partitioning analysis (RPA) class (III-IV vs. V) [21], advanced neuro-imaging (with vs. without), extent of surgery (complete resection vs. others), chemotherapy (ACNU vs. other), and radiation modality (HDT vs. CRT).

Factors with a probability value of less than 0.05 on univariate analysis were selected for testing in the multivariate analysis. Results are expressed with relative risk and a 95% confidence interval (CI).

Results

The characteristics of the 67 patients are summarized in Table 1. Included in the analysis were 34 men and 33 women aged 31 to 84 years (median, 59.0 years). Surgical resection resulted in complete resection of the tumour in 13 (19%), partial resection in 47 (70%), and biopsy in 7 (10%) patients. Forty-seven (70%) patients received chemotherapy with ACNU or other agents. Thirty-two (48%) received HDT and thirty-five (52%) received CRT; consequently, all 67 patients received either one or the other type of radiotherapy. There were 6 (9%) patients with a WHO PS of 0, 30 (45%) with a PS of 1, 12 (18%) with a PS of 2, 10 (15%) with a PS of 3, and 9 (13%) with a PS of 4. Whereas 9 patients (13%) were categorized as having the best GBM prognosis (class III), 21 (31%) were in class IV, and 37 (55%) were in class V, according to the EORTC-RPA classification system.

Nine patients were alive at the time of analysis with a mean follow-up time of 21.4 (range 1.0–71.2) months. The median OS for all patients was 17.7 months (95% CI, 14.6 – 20.9). The one- and two-year survival rates were 67.2% and 33.7%, respectively. The median progression-free survival time in this series was 7.8 months (95% CI, 5.7 – 9.9). The one- and two-year progression-free survival rates were 32.6 and 18.4%, respectively.

The univariate and multivariate analyses of prognostic factors in this study are shown in Tables 2 and 3, respectively. The multivariate analysis revealed radiation modality and EORTC RPA class as significant prognostic factors. The median OS was 24.4 months (95% CI, 18.2 – 30.5) for patients treated with HDT, compared with 14.2 months (95% CI, 10.0 – 18.3) for those treated with CRT (Fig. 1). Other previously reported prognostic factors such as age, sex, preoperative PS, treatment with or without advanced neuro-imaging, extent of surgery, and regimen of chemotherapy were not statistically significant according to the multivariate analysis. The median OS was 18.5 months (95% CI, 9.9 – 27.1) in patients 65 years and older, compared with 16.8 months (95% CI, 13.6 – 20.1) in those 64 years and younger (p=0.871).

Patients who were treated with HDT had a significantly better preoperative PS than patients treated with CRT (p=0.025). Similarly, patients who were treated with HDT were more likely to have undergone complete resection than patients treated with CRT (28.1% compared to 11.4%; p=0.078) and were more likely to be categorized in the better prognostic group (III-IV compared to V;

p=0.059); however, neither of these differences were statistically significant. Other clinical characteristics, i.e. age, sex, advanced neuro-imaging, and regimen of chemotherapy were not found to differ between patients who underwent HDT and those treated with CRT (Table 4).

Discussion

The median OS for all patients was 17.7 months; a longer median OS of 24.4 months was seen in the HDT group, compared to 14.2 months in the CRT group. Receiving either HDT or CRT was also factored out as a significant independent prognostic factor. The survival data for the CRT patients in this study were comparable to those of previous reports of patients treated with the standard therapies. Patient selection (e.g., age, PS, etc.) for the HDT group appeared not to be a major factor influencing survival time, nor did it negatively influence the survival time of the CRT patients.

It is generally accepted that the concomitant and adjuvant use of temozolomide with conventional fractionated photon radiotherapy can be effective for treating post-operative GBM with minimal additional toxicity, and a significant survival advantage has been demonstrated for this approach compared to the administration of radiotherapy alone. The median OS in this RCT reported was 14.6 months with temozolomide-plus-radiotherapy, and 12.1 months with radiotherapy alone [8]. The median OS of CRT patients observed in this study was comparable to that of patients in the temozolomide treatment arm, whereas the median OS of all patients in this study was longer than that

of the patients in the temozolomide treatment arm. The patient characteristic data from the report by Stupp and colleagues showed that patients in the temozolomide treatment arm tended to be younger and better PS (0-1) populations, and belong to less-high risk (EORTC-RPA class V) populations (Table 5). These findings suggest that the favorable survival data of all patients and those of patients who underwent HDT in this study were unlikely to reflect patient selection alone. However, better extent of surgery (complete resection; 39% compared to 19%), more-moderate risk (EORTC-RPA class IV; 53% compared to 31%) populations, aggressive salvage treatment, and other indeterminate factors e.g. surgical technique, administration of standard care etc. may have positively influenced the survival data. Additionally, small sample size, inconsistent and non-controlled patient characteristics, may have affected the results and thus pose limitations on the findings of the present study.

Here, the median OS of GBM patients increased from 15.2 months (95% CI, 8.1 – 22.3) between 1982 and 1997 to 17.7 months (95% CI, 14.6 – 20.9) between 1998 and 2007, although this trend was not statistically significant (p=0.086). The 2-year relative survival rate also increased from 23.6% between 1982 and 1997 to 33.7% between 1998 and 2007. Advancements in surgical techniques such as fluorescence guidance (since 1999) and in neuronavigation (since 2005), as well as improvements in chemotherapeutic agents, have been implemented at our institute; however, no significant differences in the extent of surgery or chemotherapy regimen were observed between

these two periods of time (i.e., pre-, post-1998). There remains no reliable evidence supporting these surgical approach and chemotherapy regimen as regards OS. Therefore, the improvements in OS may not have been related to surgical approach, but rather to changes made to the BNCT protocol since 1998 and those made to the PT protocol since 2001, when rotating gantries and regular daily fractionation became possible.

In BNCT series, acute toxicities such as mild erythema (commonly observed), transient orbital swelling in 1 patient (6.7 %) were observed. On the other hand, No late toxicity was observed in the follow-up periods. In PT series, acute toxicities such as radiation dermatitis (commonly observed), rash in 1 patient (5.9 %), and headache in 5 patients (29.4 %) were observed. As for late toxicity, radiation necrosis in 1 patient (5.9 %) and leukoencephalopathy in 1 patient (5.9 %) were observed [14, 15]. Although these data indicate that toxicity in our HDT protocol seems to be acceptable at the analysis, incidence of late toxicities of survivors such as radiation necrosis and leukoencephalopathy remains to be monitored and clarified in longer follow-up time.

Patient age has been reported as a strong prognostic factor in the treatment of GBM. In the RPA of EORTC, being 50 years old or older is a significant prognostic factor in the categorization of disease. However, in the present study, no correlation was found between age and prognosis. Recently, significant improvement in the survival of elderly patients with GBM has been observed with the introduction of aggressive treatments [23-25]. In the present series, almost no statistically significant

difference was observed in age-related survival probability. The mean age of PT and BNCT patients was 57 and 60 years, respectively. Aggressive treatment of elderly patients with GBM at our institute appears to have minimized the difference in age-related survival probability.

Patients who were treated with HDT had a better preoperative PS and were more likely to have undergone complete resection than patients treated with CRT. It was not possible to separate the effects of HDT from the selection bias toward patients with a better prognosis, because the inclusion criteria of our HDT modalities, which are based on the characteristics of GBM patients, involve the restriction of PS and the limitations of tumour size and location, both of which are correlated with the difficulty of resection. However, even in patients categorized in the worst prognostic group (EORTC-RPA class V), OS was significantly prolonged for those who had received HDT compared to those treated with CRT ($p=0.007$). Similarly, among patients who underwent partial resection and biopsy, the OS was also significantly prolonged for those who received HDT versus those treated with CRT ($p=0.005$). These results indicate that the survival benefits of HDT appear unlikely to reflect patient selection alone.

Conclusions

It is generally accepted that both the size and location of a tumour, as well as patient performance status, should be considered in evaluations of the safety and efficacy of high-dose particle

radiotherapies. In this study, patients selected to receive HDT showed longer survival times compared than those treated with CRT. Although HDT, compared to CRT, was factored out as a significant favorable prognostic factor, other major prognostic factors did not appear to be confounding. The results of this study suggest that the relatively positive survival data of patients selected to undergo HDT are unlikely to reflect patient selection alone. Randomized trials with strictly controlled inclusion criteria for the comparable selection of patients are required to demonstrate conclusively that prolonged survival is a result of these high-dose radiotherapies.

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Figure legends

Figure 1

Kaplan-Meier estimates of overall survival according to radiation modality. The hazard ratio for death among patients treated with high-dose radiotherapy, as compared to that among patients treated with conventional fractionated photon radiotherapy, was 0.44 (95% CI, 0.26– 0.76; $p<0.01$).

Table 1

Characteristics of 68 patients with glioblastoma multiforme

* Advanced neuro-imaging indicates 5-aminolevulinic-acid-induced fluorescence guidance and neuronavigation

**Radiation Therapy Oncology Group (RTOG)-RPA class VI patients were included in EORTC-RPA class V

Table 2

Univariate analysis of prognostic factors for the survival of patients with glioblastoma multiforme

Table 3

Multivariate analysis of prognostic factors for the survival of patients with glioblastoma multiforme

Table 4

Clinical characteristics of patients treated with HDT compared to CRT

Table 5

Comparison of patient characteristics in the TMZ-plus-CRT arm of EORTC 26981/22981-NCIC patients and all patients in this study

* Authors calculated

References

1. Barnholtz-Sloan JS, Sloan AE, Schwartz AG. Relative survival rates and patterns of diagnosis analyzed by time period for individuals with primary malignant brain tumour, 1973-1997. J Neurosurg. 2003; 99: 458-66.

2. Tait MJ, Petrik V, Loosemore A, Bell BA, Papadopoulos MC. Survival of patients with glioblastoma multiforme has not improved between 1993 and 2004: analysis of 625 cases. Br J Neurosurg. 2007; 21 :496-500.

3. Walker MD, Alexander E, Jr., Hunt WE, MacCarty CS, Mahaley MS, Jr., Mealey J, Jr., et al. Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. A cooperative clinical trial. J Neurosurg. 1978; 49: 333-43.

4. Walker MD, Green SB, Byar DP, Alexander E, Jr., Batzdorf U, Brooks WH, et al. Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. N Engl J Med. 1980; 303: 1323-9.

5. Kristiansen K, Hagen S, Kollevold T, Torvik A, Holme I, Nesbakken R, et al. Combined modality therapy of operated astrocytomas grade III and IV. Confirmation of the value of postoperative irradiation and lack of potentiation of bleomycin on survival time: a prospective multicenter trial of the Scandinavian Glioblastoma Study Group. Cancer. 1981; 47: 649-52.

6. Sandberg-Wollheim M, Malmstrom P, Stromblad LG, Anderson H, Borgstrom S, Brun A, et al.

A randomized study of chemotherapy with procarbazine, vincristine, and lomustine with and without radiation therapy for astrocytoma grades 3 and/or 4. Cancer. 1991; 68: 22-9.

7. Andersen AP. Postoperative irradiation of glioblastomas. Results in a randomized series. Acta Radiol Oncol Radiat Phys Biol. 1978; 17: 475-84.
8. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005; 352: 987-96.
9. Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol. 2009; 10:459-66.
10. Fitzek MM, Thornton AF, Rabinov JD, Lev MH, Pardo FS, Munzenrider JE, et al. Accelerated fractionated proton/photon irradiation to 90 cobalt gray equivalent for glioblastoma multiforme: results of a phase II prospective trial. J Neurosurg. 1999; 91: 251-60.
11. Tanaka M, Ino Y, Nakagawa K, Tago M, Todo T. High-dose conformal radiotherapy for supratentorial malignant glioma: a historical comparison. Lancet Oncol. 2005;6: 953-60.
12. 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. 2006; 64: 1317-24.

13. Souhami L, Seiferheld W, Brachman D, Podgorsak EB, Werner-Wasik M, Lustig R, et al. Randomized comparison of stereotactic radiosurgery followed by conventional radiotherapy with carmustine to conventional radiotherapy with carmustine for patients with glioblastoma multiforme: report of Radiation Therapy Oncology Group 93-05 protocol. Int J Radiat Oncol Biol Phys. 2004; 60: 853-60.
14. Yamamoto T, Nakai K, Kageji T, Kumada H, Endo K, Matsuda M, et al. Boron neutron capture therapy for newly diagnosed glioblastoma. Radiother Oncol. 2009; 91: 80-4.
15. Mizumoto M, Tsuboi K, Igaki H, Yamamoto T, Takano S, Oshiro Y, et al. Phase I/II trial of hyperfractionated concomitant boost proton radiotherapy for supratentorial glioblastoma multiforme. Int J Radiat Oncol Biol Phys. 2010; 77: 98-105.
16. Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. J Neurosurg. 2001; 95: 190-8.
17. Simpson JR, Horton J, Scott C, Curran WJ, Rubin P, Fischbach J, et al. Influence of location and extent of surgical resection on survival of patients with glioblastoma multiforme: results of three consecutive Radiation Therapy Oncology Group (RTOG) clinical trials. Int J Radiat Oncol Biol Phys. 1993; 26: 239-44.

18. Walker MD, Green SB, Byar DP, Alexander E, Jr., Batzdorf U, Brooks WH, et al. Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. N Engl J Med. 1980; 303: 1323-9.

19. Jeremic B, Milicic B, Grujicic D, Dagovic A, Aleksandrovic J. Multivariate analysis of clinical prognostic factors in patients with glioblastoma multiforme treated with a combined modality approach. J Cancer Res Clin Oncol. 2003; 129: 477-84.

20. Curran WJ, Jr., Scott CB, Horton J, Nelson JS, Weinstein AS, Fischbach AJ, et al. Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. J Natl Cancer Inst. 1993; 85: 704-10.

21. Yoshikawa K, Kajiwara K, Morioka J, Fujii M, Tanaka N, Fujisawa H, et al. Improvement of functional outcome after radical surgery in glioblastoma patients: the efficacy of a navigation-guided fence-post procedure and neurophysiological monitoring. J Neurooncol. 2006; 78: 91-7.

22. Mirimanoff RO, Gorlia T, Mason W, Van den Bent MJ, Kortmann RD, Fisher B, et al. Radiotherapy and temozolomide for newly diagnosed glioblastoma: recursive partitioning analysis of the EORTC 26981/22981-NCIC CE3 phase III randomized trial. J Clin Oncol. 2006; 24: 2563-9.

23. Keime-Guibert F, Chinot O, Taillandier L, Cartalat-Carel S, Frenay M, Kantor G, et al.

Radiotherapy for glioblastoma in the elderly. N Engl J Med. 2007; 356: 1527-35.

24. Patwardhan RV, Shorter C, Willis BK, Reddy P, Smith D, Caldito GC, et al. Survival trends in elderly patients with glioblastoma multiforme: resective surgery, radiation, and chemotherapy. Surg Neurol. 2004; 62: 207-15.

25. Combs SE, Wagner J, Bischof M, Welzel T, Wagner F, Debus J, et al. Postoperative treatment of primary glioblastoma multiforme with radiation and concomitant temozolomide in elderly patients. Int J Radiat Oncol Biol Phys. 2008; 70: 987-92.

Figure 1

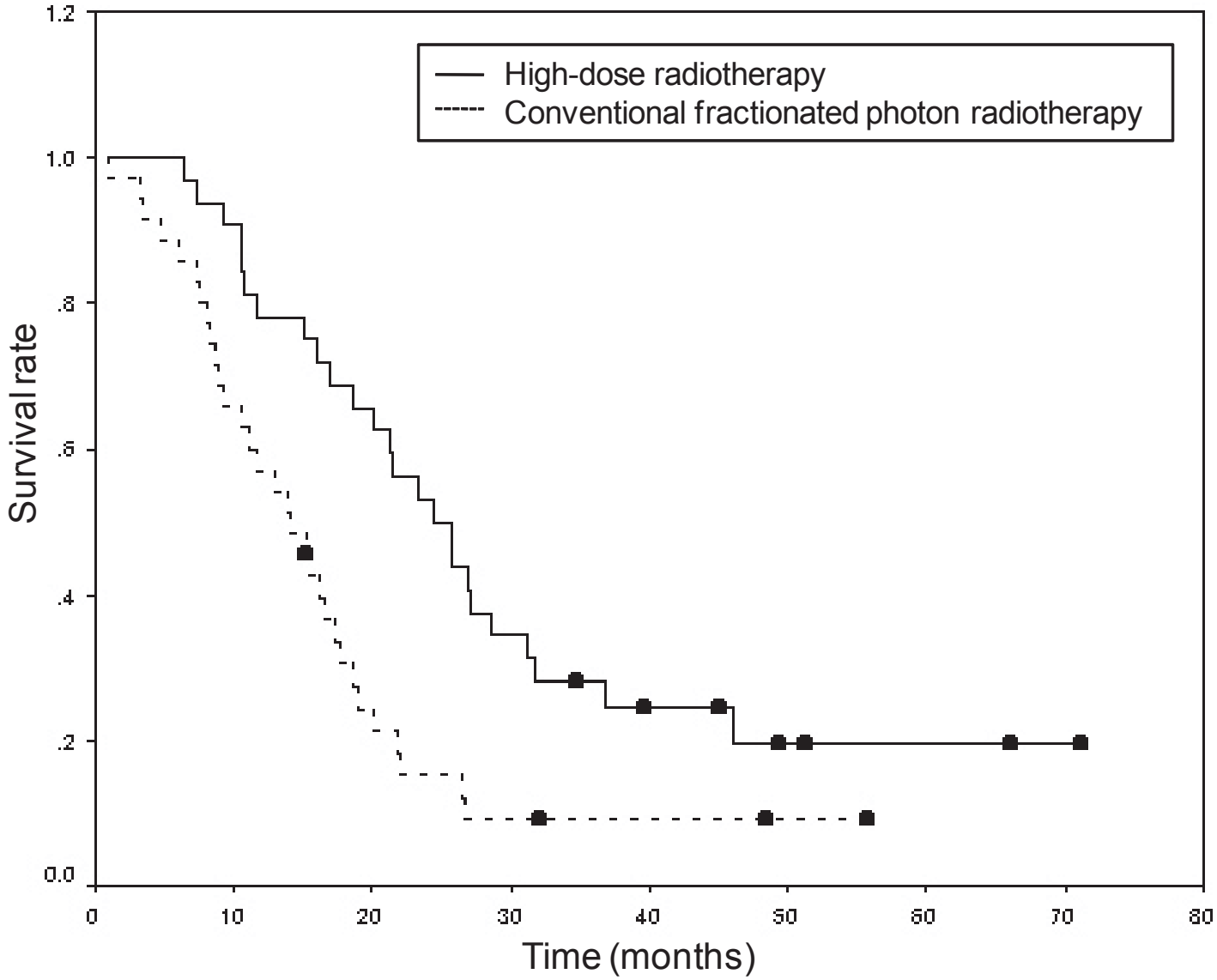
High-dose radiotherapy
Conventional fractionated photon radiotherapy
Survival rate
1.2
1.0
.8
.6
.4
.2
0.0
0
10
20
30
40
50
60
70
80
Time (months)

Table. 1

Characteristics	No. of Patients （%）
Age	
median	59.0 years
range	31 to 84 years
Sex	
male	34(51%)
female	33(49%)
Side	
left	33(49%)
right	27(40%)
midline or bilateral	7(10%)
Location	
frontal lobe	32(48%)
temporal lobe	19(28%)
parietal lobe	17(25%)
occipital lobe	1(1%)
other	6(9%)
Advanced neuro-imaging*	
yes	31(46%)
no	36(54%)
Extent of surgery	
complete	13 (19%)
partial	47 (70%)
biopsy	7 (10%)
Chemotherapy	
nimustine hydrochloride	45(67%)
other	2(3%)
none	20(30%)
Radiotherapy	
high dose	32(48%)
conventional dose	35(52%)
WHO performance status	

0	6 (9%)
1	30 (45%)
2	12 (18%)
3	10 (15%)
4	9 (13%)
EORTC-RPA class**	
III	9(13%)
IV	21(31%)
V	37(55%)

Table. 2

Variable	Hazard ratio (95% CI)	p Value
Age (<65 years vs. ≥65 years)	0.954 (0.539-1.687)	0.871
Sex (female vs. male)	0.600 (0.351-1.023)	0.061
WHO performance status (0-2 vs. 3-4)	0.525 (0.295-0.936)	0.029
EORTC-RPA class (III-IV vs. V)	0.502 (0.289-0.872)	0.014
Advanced neuro-imaging (with vs. without)	0.731 (0.430-1.244)	0.248
Extent of resection (complete vs. others)	0.735 (0.379-1.424)	0.361
Chemotherapy (ACNU vs. others)	0.632 (0.365-1.091)	0.100
Radiotherapy (high dose vs. conventional dose)	0.443 (0.258-0.762)	0.003

Table. 3

Variable	Hazard ratio (95% CI)	p Value
WHO performance status (0-2 vs. 3-4)	0.634 (0.352-1.142)	0.129
EORTC-RPA class (III-IV vs. V)	0.544 (0.310-0.954)	0.034
Radiotherapy (high dose vs. conventional dose)	0.495 (0.284-0.862)	0.013

Table. 4

Characteristics	No. of Patients (%)		p Value
	high dose	conventional dose	
age			
<65	24	22	0.210
≥65	8	13	
sex			
male	14	20	0.198
female	18	15	
Advanced neuro-imaging			
yes	14	17	0.441
no	18	18	
extent of surgery			
complete resection	9	4	0.078
others	23	31	
chemotherapy			
ACNU	21	24	0.501
others	11	11	
WHO performance status			
0-2	27	21	0.025
3-4	5	14	
EORTC-RPA class			
III-IV	18	12	0.059
V	14	23	

Table. 5

Characteristics	CRT plus TMZ	This study
Number of patients	287	67
Age		
median	56 years	59 years
range	19 to 70 years	31 to 84 years
Sex		
male	185(64%)	34(51%)
female	102(36%)	33(49%)
Extent of surgery		
complete	113 (39%)	13 (19%)
partial	126 (44%)	47 (70%)
biopsy	48 (17%)	7 (10%)
WHO performance status		
0	113 (39%)	6 (9%)
1	136 (47%)	30 (45%)
2	38 (13%)	12 (18%)
3	0 (0%)	10 (15%)
4	0 (0%)	9 (13%)
EORTC-RPA class		
III	42(15%)	9(13%)
IV	152(53%)	21(31%)
V	93(32%)	37(55%)
No. of progression	244 (85%)	59 (88%)
Salvage surgery	66* (27%)	20 (34%)
Salvage chemotherapy	142* (58%)	54 (92%)