

# Glioblastoma Treatment in the Elderly

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## Abstract

Although current treatment advances prolong patient survival, treatment for glioblastoma (GBM) in the elderly has become an emerging issue. The definition of “elderly” differs across articles; GBM predominantly occurs at an age  $\geq 65$  years, and the prognosis worsens with increasing age. Regarding molecular markers, isocitrate dehydrogenase (*IDH*) mutations are less common in the elderly with GBM. Meanwhile, O<sup>6</sup>-methylguanine DNA methyltransferase (*MGMT*) promoter methylation has been identified in approximately half of patients with GBM. Surgery should be considered as the first-line treatment even for elderly patients, and maximum safe resection is recommended if feasible. Concurrently, radiotherapy is the standard adjuvant therapy. Hypofractionated radiotherapy (e.g., 40 Gy/15 Fr) is suitable for elderly patients. Studies also supported the concurrent use of temozolomide (TMZ) with radiotherapy. In cases wherein elderly patients cannot tolerate chemoradiation, TMZ monotherapy is an effective option when *MGMT* promoter methylation is verified. Conversely, tumors with *MGMT* unmethylated promoter may be treated with radiotherapy alone to reduce the possible toxicity of TMZ. Meanwhile, the efficacy of bevacizumab (BEV) in elderly patients remains unclear. Similarly, further studies on the efficacy of carmustine wafers are needed. Based on current knowledge, we propose a treatment diagram for GBM in the elderly.

Key words: glioblastoma, elderly, treatment, review

## Introduction

Recent treatment advances have improved the survival of patients with glioblastoma (GBM), particularly since the introduction of temozolomide (TMZ) in 2006.<sup>1)</sup> However, old age remains among the most significant factors associated with poor prognosis of GBM, even after the introduction of TMZ. However, to date, no standard treatment protocol has been established due to the lack of supporting evidence because trials often exclude elderly cases. In Japan, the treatment guidelines for adults with GBM have been published by the Brain Tumor Guidelines Extension Committee centered on the Japan Society for Neuro-Oncology in July 2016 and serves as a basis for treatment of the elderly with GBM. In this review, we discuss the recent literature on GBM in the elderly.

## Epidemiology of GBM in the elderly

GBM mainly occurs in patients aged  $>65$  years. The Japan Geriatric Neurosurgery Society stipulated that patients with GBM aged  $\geq 70$  years are regarded as “elderly.” However, many studies abroad discussing GBM in the elderly include patients younger than 70 years (e.g., 60 years). An accurate definition has not been established to date. Thus, the definition of “elderly” varies across articles.

Published statistics from the Japan Brain Tumor Registry from 2001 to 2004 illustrated the following tissue histology (based on the World Health Organization (WHO) classification in 2007): GBM 10.8%, anaplastic astrocytoma 3.8%, anaplastic oligodendroglioma 0.8%, and anaplastic oligoastrocytoma 0.9%. In GBM, median overall survival (OS) was 15 months, with a 5-year OS of 9.9%. Median progression-free survival (PFS) was 8.1 months, with a 5-year PFS of 9.3%. However, the above statistics were collected before the introduction of TMZ. A large proportion of patients with GBM were elderly. Patients aged  $>50$  years accounted for 78% of the total cases, with those aged  $>65$  years and  $>75$  years accounting for 42% and 11.4%, respectively. Based on the

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statistics, the most frequent age group of patients was 65–69 years, which accounted for 17% of the cases.<sup>2)</sup> Statistics from Kumamoto, Japan (1980–1995) demonstrated a high incidence of malignant glioma in the elderly population. The incidence of GBM in those aged <70 years was 1.42/100,000 person-years, whereas the incidence was 2.40/100,000 person-years in patients aged ≥70 years. Despite the increasing incidence of GBM in the elderly, these patients are less likely to undergo histopathological examinations. Pathological diagnosis was made in 79.7% of young patients and 69.4% of elderly patients.<sup>3)</sup> The elderly are more likely to be treated as GBM without histopathological verification.<sup>4)</sup>

With increasing age, the survival prognosis worsens without any clear borderline. Survival in elderly patients is short even in those who receive multimodal treatment with surgical resection, radiotherapy, and chemotherapy.<sup>4)</sup> Active treatment would be beneficial to elderly patients. Surgical resection prolongs survival, even in elderly patients aged ≥80 years.<sup>5)</sup> Radiotherapy with concurrent TMZ after surgery is associated with improved survival even in elderly patients aged >75 years.<sup>6)</sup> Although age is a poor prognostic factor, old age alone is suggested to have no association with poor prognosis.<sup>7,8)</sup> Radiotherapy with TMZ significantly reduced the mortality risk by 55% even in elderly patients, indicating that aggressive treatment should not be withheld because of old age.<sup>7)</sup>

## Molecular Characteristics

### IDH mutation

The most distinct difference in molecular characteristics of GBM between the young and elderly is CpG island methylator phenotype (G-CIMP) and isocitrate dehydrogenase (*IDH*) mutation. The Cancer Genome Atlas project determined the profile of promoter DNA methylation alterations in GBM. A subset of primary GBMs exhibit the glioma-G-CIMP, characterized by widespread DNA hypermethylation of a large number of CpG islands.<sup>9)</sup> G-CIMP is strongly associated with mutations of *IDH1*. *IDH1* mutation induces DNA hypermethylation to reshaping the methylome to resemble that of the CIMP phenotype. The genome-wide genetic and epigenetic alterations resulting from mutant *IDH* activate key gene expression programs, characterize G-CIMP-positive proneural GBM exclusively, and are predictive of favorable survival.<sup>10)</sup> In G-CIMP-negative GBMs, age is an independent prognostic factor.<sup>11)</sup> In the WHO classification of central nervous system (CNS) tumor 2016, GBMs are subdivided according to their molecular phenotype, namely, *IDH* wild type and *IDH* mutant, based on diverse

and distinct patterns of tumorigenesis and clinical significance.<sup>12)</sup> *IDH* mutation is considered to be an early event in tumorigenesis of low-grade glioma.<sup>13)</sup> *IDH* gene mutation occurs in 88% of secondary GBM, and GBM *IDH* mutant is more frequently diagnosed among young patients (mean age, 45 years at diagnosis) but accounts for only 5% of all GBM cases.<sup>14)</sup> Meanwhile, primary GBM, which exhibits a low frequency or absence of *IDH* mutation, is the most predominant GBM in the elderly. Accordingly, *IDH* mutation in GBM in the elderly is less commonly identified (2.4–6%).<sup>13–17)</sup> Age-adjusted multivariate analysis previously suggested that the better prognosis of secondary GBM is due to the young age rather than the difference in biological behavior of the tumor.<sup>14)</sup> Prognostic significance has recently become an issue mainly due to the predominant occurrence of *IDH1* mutations in young patients.<sup>17)</sup> A meta-analysis of GBM focusing on *IDH* mutation demonstrated a prognostic impact of *IDH* on the OS of GBM patients (HR: 0.45).<sup>18)</sup>

### MGMT promoter methylation status

O<sup>6</sup>-methylguanine DNA methyltransferase (MGMT) is a DNA repair enzyme targeting DNA damage, which leads to cellular resistance to alkylating chemotherapeutic agents targeting the O<sup>6</sup> position of guanine such as TMZ. Hypermethylation of *MGMT* promoter downregulates the normal DNA repair mechanism by MGMT enzyme, making the tumor more susceptible to radiation or chemotherapy with an alkylating agent. Hegi et al. found that inactivation of *MGMT* by its promoter methylation improved the survival outcome of GBM patients treated with TMZ.<sup>19)</sup> *MGMT* promoter methylation is predominantly identified in astrocytic and oligodendroglial tumor with *IDH* mutations, although primary GBM with *MGMT* promoter methylation had no *IDH* mutation. *MGMT* methylation may occur as part of the G-CIMP phenotype, associating with the presence of *IDH1/2* mutations. *MGMT* promoter methylation and *IDH* mutation are suggested to be among the earliest events in the tumorigenesis of low-grade glioma.<sup>20)</sup> *MGMT* promoter methylation was detected in approximately half (35–57.5%) of GBM in the elderly.<sup>21–23)</sup> The methylation status of the *MGMT* promoter was not influenced by age, sex, and Karnofsky Performance Status (KPS).<sup>20,24)</sup> A meta-analysis also indicated that *MGMT* promoter methylation is independent of age, with 47% in the elderly and 44% in young patients with GBM.<sup>25)</sup>

### Other molecular characteristics

Analysis of collective data from systematic search of MEDLINE (1998–2010) revealed that *MGMT*

promoter methylation and *IDH* mutation were prognostic factors, but known molecular players, such as epidermal growth factor receptor (EGFR), *p53*, *CDKN2A*, and *PTEN* were not prognostic factors in GBM.<sup>11)</sup> Molecular deregulation related to the hypoxic response and angiogenesis including vascular endothelial growth factor (VEGF) was higher in GBM in the elderly than in young patients, suggesting two different biological and clinical behaviors.<sup>26)</sup> The prognostic value of telomerase reverse transcriptase (*TERT*) promoter mutation in GBM has been debated. A recent study reported that altered *TERT* expression caused by activating mutations of the rs2853669 polymorphism within the *TERT* promoter region is significantly associated with poor prognosis in young patients with GBM but not in the elderly. GBM in the elderly has high *TERT* mRNA levels and reduced telomere lengths.<sup>24)</sup> A domestic collaborative study showed that patients with *TERT* mutant-*MGMT* unmethylated GBM have the worst prognosis, which is validated by multivariate analysis incorporating age, sex, cohort, KPS, tumor location, surgical history, *TERT*, and *MGMT*.<sup>27)</sup>

## Clinical Aspects

### Surgery

Surgical removal within the safety margin prolongs OS, delays tumor growth, and improves functional outcomes. Although a prospective randomized study conducted by Vuorinen et al. only enrolled a small number of patients, it is the only randomized study to discuss the extent of resection in elderly patients with malignant GBM aged >65

years. Surgical removal of the tumor prolonged survival by 2.8 times than biopsy (median OS: 171 days after the craniotomy versus 85 days after the biopsy), whereas no significant difference was observed in the time of deterioration between these two treatment arms.<sup>28)</sup> There have been many surgical series demonstrating the survival advantage of gross total resection (GTR) compared to the biopsy (Table 1).<sup>15,28–32)</sup> Almenawer investigated the optimal range of resection in patients with malignant glioma aged ≥60 years. The result of meta-analysis including 34 studies showed that surgical resection was superior to biopsy in OS (mean difference 3.88 months, 95% CI: 2.14–5.62,  $P < 0.001$ ), PFS, postoperative KPS, and mortality, although the difference was unclear for morbidity. GTR of the tumor was significantly superior to subtotal resection (STR) in terms of OS (mean difference 3.77 months, 95% CI: 2.26–5.29,  $P < 0.001$ ), PFS, and postoperative KPS. Surgical extension did not improve mortality and morbidity. Similar to young patients, maximum surgical resection within a safe range would result in prolonged survival, delayed tumor progression, and improved functional prognosis (Table 1).<sup>32)</sup> Epidemiological study of 20,705 adult patients with GBM in the Surveillance, Epidemiology, and End Results registry (1998–2009) illustrated a stepwise decrease of GTR with increasing age, although, GTR had a significantly better prognosis irrespective of gender and race, tumor site and size, and radiotherapy. Compared with STR, GTR extended survival by 2 months in patients aged ≥75 years.<sup>33)</sup>

The surgery is aimed at, first, achieving maximal cytoreduction of the tumor. Resection as much as

**Table 1** Surgical series for elderly patients with GBM

Author Year	N	Age	Surgery	OS (months)	95% CI	Note
Vuorinen <sup>28)</sup> 2003	30	>65	Resection Biopsy	171 days 85 days	146–278 55–157	Randomized controlled trial
Scott <sup>29)</sup> 2011	206	≥70	GTR STR Biopsy	10.7 6.9 2.8	NA	
Hoffermann <sup>30)</sup> 2015	124	≥65	GTR STR Partial Biopsy	15.0 11.0 6.4 5.6	11.4–18.7 7.9–14.2 4.1–8.8 3.4–7.8	
Lombardi <sup>15)</sup> 2015	237	≥65	GTR STR	17.7 16.1	14.9–21.2 11.6–21.07	
Babu <sup>31)</sup> 2016	120	≥65	GTR STR	14.1 9.6	NA	
Almenawer <sup>32)</sup> 2015	12607	≥60	GTR STR Biopsy	14.04 8.68 5.71	12.8–15.2 7.87–9.48 5.04–6.36	Meta-analysis of 34 studies

GTR: gross total removal, STR: subtotal removal, OS: overall survival.

possible is associated with favorable prognosis even in elderly patients with GBM. The second aim is to obtain histopathological diagnosis of GBM. Ring-shaped lesions need to be examined to rule out metastatic tumors, abscess, and inflammatory diseases because a report showed that 20% of lesions believed as GBM turned out to be other lesions.<sup>33)</sup> In addition to histological diagnosis, information regarding molecular markers, such as *IDH* mutation and *MGMT* methylation status, is necessary to develop a treatment strategy.

## Radiotherapy

Radiotherapy is an effective treatment for elderly patients with GBM. The ANOCEF trial is a randomized controlled trial comparing radiotherapy (50 Gy, 1.8 Gy/day) treatment with best supportive care in patients with malignant glioma aged  $\geq 70$  years with preserved performance status (KPS  $\geq 70$ ). The study was terminated because the superiority of the radiotherapy group was clarified in the interim analysis (median OS: 29.1 weeks versus 16.9 weeks). Irradiation did not result in a significant difference of deterioration of quality of life (QOL) and cognitive function (Table 2).<sup>34)</sup> Roa et al. conducted a randomized controlled trial comparing standard radiotherapy (Std-RT, 60 Gy/30 Fr) with hypofractionated radiotherapy (Hypo-RT, 40 Gy/15 Fr) for 100 postsurgical patients with GBM aged  $\geq 60$  years. OS between Std-RT and Hypo-RT (5.1 and 5.6 months, respectively) was not significantly different (Tables 2, 3). No difference was also noted in KPS, but steroid use was more frequent in the Std-RT.<sup>35)</sup> In the subset analysis of International Atomic Energy Agency randomized phase III trial<sup>36)</sup> restricted to elderly and/or frail patients with GBM, further lower-dose radiotherapy of 25 Gy/5 fr demonstrated similar benefit on OS as 40 Gy/15 fr (6.8 months for 25 Gy/5 fr and 6.2 month for 40 Gy/15 fr, respectively) (Tables 2, 3).<sup>37)</sup> The Nordic trial is a randomized phase III trial comparing Std-RT (60 Gy/30 Fr), Hypo-RT (34 Gy/10 Fr), and TMZ monotherapy in elderly patients with GBM aged  $\geq 60$  years. The study revealed that Hypo-RT is an effective and reasonable treatment even for elderly patients with GBM aged  $>70$  years (median OS: 7.0 months for Hypo-RT versus 5.2 months for Std-RT) (Table 3). No significant difference was noted in survival according to *MGMT* promoter methylation status when patients are treated with radiotherapy alone, which is also equivalent to TMZ treatment alone in patients with *MGMT* unmethylated promoter (median OS: 7.0 months for RT and 6.8 months for TMZ) (Table 2).<sup>23)</sup> Minniti et al. retrospectively studied patients with GBM aged  $\geq 65$  years treated with Std-RT

(60 Gy/30 Fr) versus Hypo-RT (40 Gy/15 Fr) both with concomitant and adjuvant TMZ. Median OS and PFS did not differ between the two treatment arms (12 and 5.6 months for Std-RT, and 12.5 and 6.7 months for Hypo-RT, respectively) (Table 3). However, Std-RT with TMZ was associated with a significant increase in grade 2 and 3 neurological toxicity, decreased KPS scores, and high steroid requirement.<sup>38)</sup>

Collectively, the results of various studies indicate that Hypo-RT for elderly patients with GBM leads to similar survival benefit as that of Std-RT but with less neurotoxicity and steroid administration and short treatment time and hospitalization period. The clinical practice guideline of radiation therapy for GBM was published by the American Society for Radiation Oncology in 2016. The guidelines state that patients with GBM aged  $<70$  years who have a reasonable performance status should receive Std-RT (e.g., 60 Gy/30 Fr) with concurrent and adjuvant TMZ. Meanwhile, elderly patients aged  $\geq 70$  years with reasonable performance status should receive Hypo-RT (e.g., 40 Gy/15 Fr). Because there is a lack of evidence that Std-RT is more efficacious than Hypo-RT.<sup>39)</sup>

## Chemotherapy

### 1. Temozolomide

TMZ is a standard first-line chemotherapeutic agent for GBM. The EORTC-NCIC trial by Stupp et al. only included patients with GBM aged up to 70 years.<sup>1,40)</sup> Therefore, the optimal treatment of GBM in patients aged over 70 years remains unclear.

The NOA-08 trial exhibited non-inferiority of TMZ monotherapy to radiotherapy. The dose-dense TMZ monotherapy (100 mg/m<sup>2</sup>/day; 1 week on/1 week off) demonstrated a median survival of 8.6 months with TMZ monotherapy comparable to 9.6 months with the Std-RT (HR: 1.09). OS was significantly longer in patients with *MGMT* promoter methylation than in *MGMT* unmethylated (11.9 months versus 8.2 months, respectively; HR: 0.62). The study suggested that elderly patients with *MGMT* promoter methylation should not be treated with radiotherapy alone (Table 2).<sup>22)</sup> In the Nordic trial, TMZ monotherapy (200 mg/m<sup>2</sup>/day, 5 days on/23 days off) and two different schedules of radiotherapy alone were compared. TMZ monotherapy exhibited superior OS to the radiotherapy alone (8.3 months for TMZ monotherapy; 7.5 and 6.0 months for Hypo-RT and Std-RT, respectively, in GBM patients aged  $>60$  years). In a subset of GBM patients aged  $>70$  years, OS reached 9.0 months for TMZ monotherapy and 7.0 and 5.2 months for Hypo-RT and Std-RT, respectively. In particular,

**Table 2** Randomized controlled trials for elderly patients with GBM

Study	Age (years)	N	Treatment	Median OS (95% CI)	Hazard Ratio (95% CI)	Note
<b>Surgery</b>						
Vuorinen 2003 <sup>28)</sup>	>65	30	Biopsy + RT Resection + RT	85 days 171 days	2.621 (1.035–6.641)	Resection improves survival
<b>Radiotherapy</b>						
Keime-Guibert 2007 <sup>34)</sup>	≥70	85	Resection + best supportive care Resection + RT	16.9 weeks 29.1 weeks	0.47 (0.29–0.76)	ANOCEF trial RT improves survival
Roa 2004 <sup>35)</sup>	≥60	100	Std RT (60 Gy/30 Fr) Hypo-RT (40 Gy/15 Fr)	5.1 months 5.6 months	0.89 (0.59–1.36)	Non-inferiority of Hypo-RT
Roa 2015 <sup>36)</sup>	≥50 + frail ≥65	98	Std-RT (Hypo-RT) (40 Gy/15 Fr) Hypo-RT (short-course) (25 Gy/5 Fr)	6.4 months (5.1–7.6) 7.9 months (9.3–9.6)	NA	IAEA E33033 trial. Frail: KPS 50–70
Guedes de Castro 2017 <sup>37)</sup>	≥65	61	Std-RT (Hypo-RT) (40 Gy/15 Fr) Hypo-RT (short-course) (25 Gy/5 Fr)	6.2 months (5.1–7.6) 6.8 months (9.3–9.6)	NA	Subset analysis of IAEA trial
<b>Radiation-Chemotherapy</b>						
Wick 2012 <sup>22)</sup>	>65	412	Std-RT (60 Gy/30 Fr) Dose dense TMZ* (100 mg/m <sup>2</sup> /day, 1-week) MGMT unmethylated MGMT methylated	9.6 months 8.6 months 8.2 months 11.9 months	1.09 (0.84–1.42) 0.62 (0.42–0.91)	NOA-08 trial Non-inferiority of the dose dense TMZ. MGMT methylation associated with longer OS
Malmström 2012 <sup>23)</sup>	≥60	342	Std-RT (60 Gy/30 Fr) Hypo-RT (34 Gy/10 Fr) Any radiotherapy MGMT unmethylated MGMT methylated TMZ monotherapy MGMT unmethylated MGMT methylated	6.0 months 7.5 months 7.0 months 8.2 months 8.3 months 6.8 months 9.7 months	0.85 (0.64–1.12) 0.97 (0.69–1.38) 0.7 (0.52–0.93) 0.56 (0.34–0.93)	Nordic trial MGMT promoter methylation status to predict clinical benefit of TMZ but not in RT. More benefit of TMZ monotherapy in GBM aged >70
Perry 2016 <sup>43)</sup>	≥65	562	Hypo-RT alone MGMT unmethylated MGMT methylated Hypo RT + TMZ (3 weeks) MGMT unmethylated MGMT methylated	7.6 months 7.9 months 7.7 months 9.3 months 10.0 months 13.5 months	0.67 (0.56–0.80) 0.75 (0.56–1.01) 0.53 (0.38–0.73)	CCTG CE.6 trial. Improvement of OS by addition of TMZ to Hypo-RT for all cases

GBM: glioblastoma, KPS: Karnofsky Performance Status, MGMT: O<sup>6</sup>-methylguanine DNA methyltransferase, MGMT unmethylated: absence of *MGMT* promoter methylation, MGMT methylated: presence of *MGMT* promoter methylation, OS: overall survival, Std-RT: Standard radiotherapy, Hypo-RT: Hypofractionated radiotherapy, RT: radiotherapy, TMZ: temozolomide. \*Dose-dense TMZ: 100 mg/m<sup>2</sup>/day, 1-week on/1-week off regimen.

**Table 3 Studies comparing standard and hypofractionated radiotherapy in elderly patients with GBM**

Author Year	Age	N	OS (month) Std-RT	OS (month) Hypo-RT	Hazard ratio (95% CI)	P
Roa 2004 <sup>35)</sup>	≥60 years	100	5.1	5.6	0.89 (0.59–1.36)	0.57
Malmström 2012 <sup>23)</sup>	60–70 years	198	7.6	8.8	1.06 (0.73–1.54)	0.77
	>70 years	81	5.2	7.0	0.59 (0.37–0.93)	0.02
Minniti 2015 <sup>38)</sup>	≥65 years	329	12.0	12.5	0.93 (0.66–1.31)	0.500
	propensity matched analysis	90				0.70
Guedes de Castro* 2017 <sup>37)</sup>	≥65 years	61	6.2	6.8	NA	0.936
	≥65 years, KPS 50–70	40	6.7	7.5		0.904
	≥65 years, KPS >80	21	8.0	8.0		0.890

Hypo-RT: hypofractionated radiotherapy, KPS: Karnofsky performance status, OS: overall survival, Std-RT: standard radiotherapy. \*Lower-dose radiotherapy: 40 Gy/15 fr for Std-RT and 25 Gy/5 fr for Hypo-RT.

*MGMT* promoter methylation status predicted TMZ response, indicating median OS of 9.7 months for *MGMT* methylated promoter and 6.8 months for *MGMT* unmethylated promoter (Table 2). In the TMZ group, hematological complications of grade III/IV neutropenia and thrombocytopenia were observed, but QOL was superior while the global health status was equivalent with that of radiotherapy alone.<sup>23)</sup> A meta-analysis of 16 nonrandomized controlled trials demonstrated that radiotherapy plus TMZ decreased the mortality risk (HR: 0.59) and disease progression (HR: 0.58). The survival benefit of radiotherapy plus TMZ was evident in elderly patients with GBM with a favorable prognosis (e.g., extensive resection and favorable KPS). More frequent toxicities in radiotherapy plus TMZ were observed, particularly in hematological toxicities, although these were deemed acceptable.<sup>25)</sup> Treatment with TMZ-based chemotherapy improved OS in elderly patients with GBM with *MGMT* promoter methylation (HR: 0.49). The TMZ-containing regimen was superior to radiation alone in elderly patients with GBM with *MGMT* promoter methylation (HR: 0.48) but not in those with *MGMT* unmethylated promoter (HR: 1.14).<sup>41)</sup> Another meta-analysis by Zarnett concluded that TMZ monotherapy or Hypo-RT alone may be considered in elderly patients with GBM who are poor candidates to undergo radiochemotherapy. In patients with *MGMT* promoter methylation, TMZ monotherapy is more beneficial than radiation monotherapy. Based on this result, their recommendations are as follows: Level 1A: Either single-agent TMZ or hypofractionated radiotherapy alone may be used for the treatment of elderly patients with GBM multiforme who are not candidates for combined radiotherapy and chemotherapy. Level 1B:

Elderly patients who have *MGMT* promoter methylation are likely to benefit from TMZ alone over radiotherapy. However, evidence to recommend either TMZ alone or radiotherapy alone in patients with *MGMT* unmethylated promoter are lacking.<sup>42)</sup>

The result of many trials showed *MGMT* promoter methylation status as a useful prognostic biomarker to predict the survival of GBM in the elderly, particularly in patients treated with TMZ, whereas survival benefit from TMZ is unclear in patients with *MGMT* unmethylated promoter.<sup>21)</sup> CCTG CE.6, EORTC 26062-22061, the most recently published randomized controlled trial, elucidated this issue. The study included 562 patients with GBM aged ≥65 years and compared Hypo-RT (40 Gy/15 Fr) alone versus Hypo-RT with 3 weeks of concomitant TMZ plus monthly adjuvant TMZ until progression or completion of 12 cycles. Combining TMZ with Hypo-RT was tolerable and resulted in prolonged OS and PFS in all GBM patient groups. Hypo-RT plus TMZ was superior in median OS and PFS than radiation alone (9.3 and 5.3 months versus 7.6 and 3.9 months, respectively; HR: 0.67 for OS and 0.50 for PFS). Patients with *MGMT* promoter methylation treated with radiotherapy plus TMZ demonstrated significantly longer survival than those treated with radiotherapy alone (13.5 months versus 7.7 months; HR: 0.53). Moreover, patients with GBM with *MGMT* unmethylated promoter treated with radiotherapy plus TMZ survived longer than those treated with radiotherapy alone (10.0 months versus 7.9 months; HR: 0.75). Interestingly, younger patients received less benefit by Hypo-RT with TMZ. By age group, median OS of Hypo-RT with TMZ versus Hypo-RT alone were 65–70 years: 8.7 months versus 8.3 months (HR 0.93),

71–75 years: 9.3 months versus 7.6 months (HR 0.63), and  $\geq 76$  years: 10.0 months versus 7.1 months (HR 0.53), respectively. No difference was noted in QOL, but patients in the radiotherapy plus TMZ group demonstrated high levels of nausea, vomiting, and constipation. Elderly patients with *MGMT* methylated tumors can expect prolonged survival from the combination of TMZ with radiotherapy. The addition of concomitant and adjuvant TMZ to Hypo-RT significantly improved OS and PFS in all elderly patients with GBM (Table 2).<sup>43)</sup>

In summary, initial treatment with TMZ combined with radiotherapy is a standard in GBM management, even in elderly patients. Reactivity to TMZ depends on the status of *MGMT* promoter methylation. Tumors with *MGMT* promoter methylation have better therapeutic response. In cases where radiochemotherapy is not feasible, TMZ monotherapy would be effective for tumors with *MGMT* promoter methylation. Moreover, in tumors with *MGMT* unmethylated promoter, adding TMZ to radiation therapy would be beneficial.

## 2. Bevacizumab

Evidence of efficacy of BEV use in elderly patients with GBM is limited. To date, published randomized studies of BEV focusing on elderly patients are yet to be published. Clinical benefits of bevacizumab use in elderly patients with GBM remain unclear.

Several studies proposed that BEV might affect PFS and possibly OS in selected elderly patients with a favorable prognosis, that is, GTR and preserved PS. The AVAglio trial was conducted for adult patients with GBM, including 73 patients aged  $\geq 70$  years. In this study, BEV resulted in prolonged PFS even in a subset of patients aged  $\geq 65$  years (HR: 0.68; 95% CI: 0.49–0.92), but this effect was decreased in patients aged  $\geq 70$  years (HR: 0.78; 95% CI: 0.46–1.33).<sup>44)</sup> The ANOCEF Phase II trial presented at the American Society of Clinical Oncology (ASCO) 2013 Annual Meeting included 66 newly identified patients with GBM who were diagnosed via biopsy, aged  $\geq 70$  years, and with KPS  $< 70$ . TMZ monotherapy with BEV demonstrated a median OS of 24 weeks, which was quite similar to the OS for TMZ monotherapy at 25 weeks. Median PFS was 16 weeks, with 25 patients (38%) becoming transiently capable of self-care. From this result, the addition of BEV in treating elderly patients with poor performance status (PS) might not be beneficial in improving OS and PFS.<sup>45)</sup> However, adding BEV in the treatment regimen for elderly patients with preserved PS and underwent gross total excision resulted in better prognosis. In the study of surgically treated 120 GBM patients

aged  $\geq 65$  years with a median KPS of 80, using BEV yielded a higher OS of 20.1 months than the 7.9 months without BEV. Multivariate stepwise analysis indicated that old age (HR: 1.06), high KPS score (HR: 0.97), and using BEV (HR: 0.51) were prognostic factors of GBM.<sup>31)</sup> The result implies that adding BEV in the treatment of selected patients with GBM might have a survival benefit.

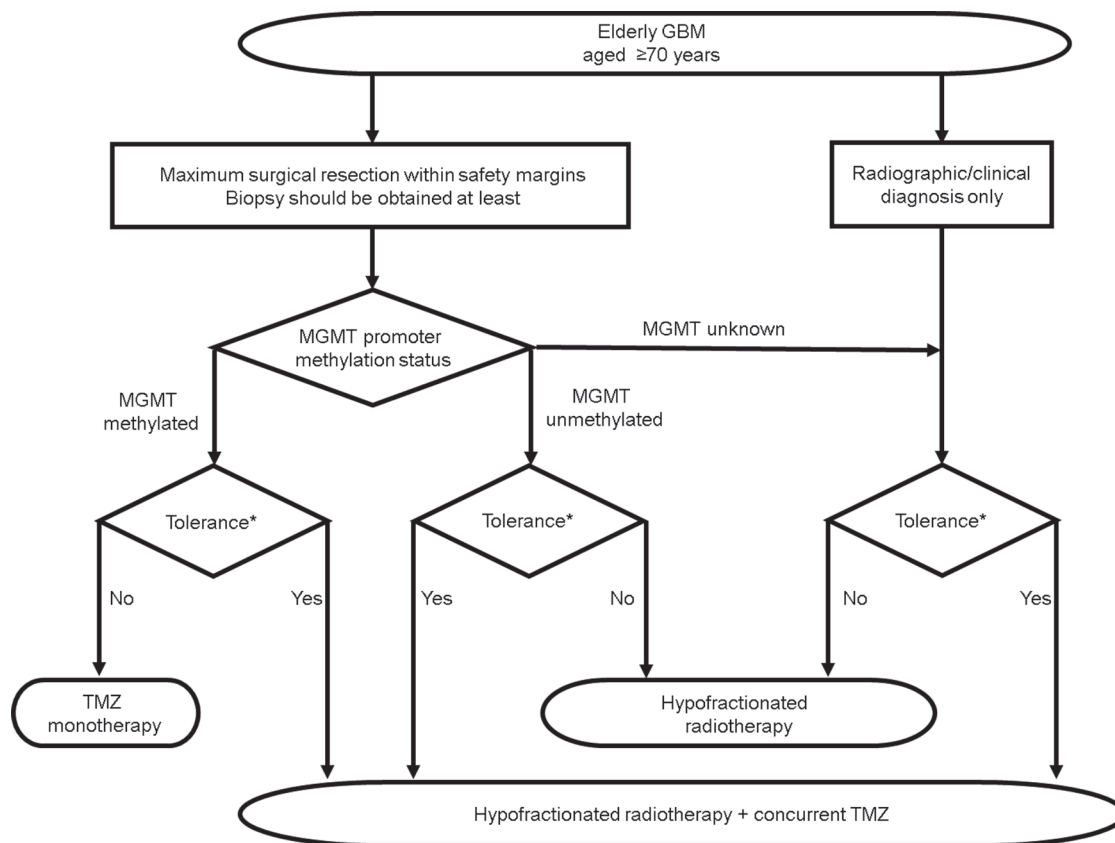
## 3. Carmustine wafer

Carmustine wafer (Gliadel wafer, Eisai Co., Ltd., Tokyo, Japan) is biodegradable polymers containing 3.85% carmustine (1,3-bis[2-chlor-oethyl]-1-nitroso-urea). No published randomized controlled trials for carmustine wafer focusing on elderly patients are available.<sup>46–50)</sup> The effect of carmustine wafer on elderly patients with GBM has been unclear. Only one case control study exhibited prolonged survival due to carmustine wafer implantation in elderly GBM aged  $\geq 65$  years, with no increase of adverse events. The use of carmustine wafers resulted in significantly prolonged OS (8.7 months with carmustine wafer and 5.5 months without wafer). A subgroup analysis demonstrated significant survival advantage of carmustine wafer implantation even in patients older than 70 years (9.1 months versus 4.8 months) and 75 years (6.0 months versus 4.7 months).<sup>49)</sup> There is a lack of evidence regarding the efficacy of carmustine wafer in elderly patients with GBM. Further investigation is needed.

## Conclusion

Based on current evidence in treating elderly patients with GBM, we propose the treatment diagram for elderly patients with GBM (Fig. 1). The results presented in the current study include those based on preliminary studies, particularly on the use of BEV and carmustine wafer. As such, further research is still necessary to establish the standard therapeutic regimen for elderly patients with GBM.

1. No accurate definition for “elderly” has been established, but an age of 70 years is one of the criteria based on the judgment of each patient’s condition.
2. Maximum surgical resection within the safety margins, if feasible, is recommended. Biopsy should be considered to make a histological diagnosis and verify the *MGMT* status.
3. For adjuvant treatment, hypofractionated radiotherapy and concurrent TMZ are recommended, regardless of the *MGMT* status.
4. TMZ monotherapy can be considered if the tumor is positive for *MGMT* promoter methylation.



**Fig. 1** Proposed flow chart for the treatment of elderly GBM. \*Tolerance to the treatment should be judged by individual patient's condition. (e.g. performance status, frailty and co-morbidities etc).

5. Hypofractionated radiotherapy alone can be considered if the tumor has an unmethylated *MGMT* promoter.

6. Using bevacizumab might be beneficial in surgically treated patients with good performance status.

7. A carmustine wafer might be beneficial to both young and elderly patients, although severe toxicity in case of concomitant use with TMZ should be closely monitored.

### Conflicts of Interest Disclosure

All authors completed a self-declaration of the conflicts of interest (COI) to the Japan Neurosurgical Society and declare no potential COI regarding this manuscript.

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