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Review Article

Review Article

Optimal managements of elderly patients with glioblastoma

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Abstract

Optimizing the management of elderly patients with glioblastoma is an ongoing task in neuro-oncology. The number of patients with this tumor type is gradually increasing with the aging of the population. Although available data and practice recommendations remain limited, the current strategy is maximal safe surgical resection followed by radiotherapy in combination with temozolomide. However, survival is significantly worse than that in the younger population. Surgical resection provides survival benefit in patients with good performance status. Hypofractionated radiotherapy decreases toxicities while maintaining therapeutic efficacy, thus improving treatment adherence and subsequently leading to better quality of life. The intensity of these treatments should be balanced with patient-specific factors and consideration of quality of life. This review discusses the current optimal management in terms of efficacy and safety, as well as future perspectives.

Key words: glioblastoma, elderly, management, surgery, radiotherapy, chemotherapy

Introduction

Glioblastoma is an aggressive primary brain tumor with a median overall survival (OS) of <18 months despite intensive treatment (1,2), falling to <12 months in elderly populations. The peak incidence of glioblastoma is in the 60s to 70s (1–3). The Japanese brain tumor registry (2005–2008) reported that glioblastomas comprised 2006 (12.0%) of 16 683 primary brain tumors and 44.6% of patients were over 65 years old (1). Initial symptoms are focal symptoms (57%), disturbance of consciousness (15%), seizure (14%) and intracranial hypertension (10%) (1). The number of elderly patients with glioblastoma is gradually increasing as the population ages (1–3), although the overall incidence of glioblastoma in the elderly remains stable (4). Elderly populations have been excluded from most clinical trials for glioblastoma because of their poor prognosis, comorbidities and the sensitivity of the aged brain to radiation (5). The cut-off age to define an elderly population differs among clinical studies, ranging between 60 and 75 years. The progression of glioblastoma impairs performance status by reducing functional and cognitive abilities, particularly among the elderly (6).

Current management for glioblastoma comprises surgery, radiotherapy and chemotherapy. For patients younger than 70 years old, the standard approach is maximal safe surgical resection followed by radiotherapy comprising 60 Gy in 30 fractions with concomitant and adjuvant temozolomide (Stupp regimen) (7,8). Some studies have shown that the Stupp regimen prolonged OS in elderly patients with good performance status (5,9–11). In a review of the United States National Cancer Database, prognostic factors were analyzed in elderly patients with glioblastoma (12). Gross total resection (GTR) was associated with the greatest survival benefit, and chemotherapy and radiotherapy also provided survival benefits. These treatment options improved outcomes regardless of performance status (12). However, all these therapies were less frequently

used in elderly patients, probably due to the risk of side effects from the treatments. Treatment-related toxicities such as neurocognitive deterioration have thus remained as critical issues. However, temozolomide was found to significantly improve outcomes among elderly patients with glioblastoma showing hypermethylation of the O6-methylguanine-DNA methyltransferase *(MGMT)* promoter (13). The National Comprehensive Cancer Network (NCCN) guidelines (Version 2.2021) define elderly patients as age > 70 years and encourage active treatments in patients with Karnofsky Performance Status (KPS) scores ≥60 (14). In elderly patients with poor performance status, KPS < 60, NCCN guidelines recommend hypofractionated radiotherapy alone, temozolomide alone or palliative/best supportive care (14).

Conventionally fractionated radiotherapy prolonged survival in elderly populations with glioblastoma, but low completion rates and declines in activities of daily living presented a dilemma (15). Hypofractionated radiotherapy has thus been developed as a means of preserving efficacy while decreasing the toxicities encountered during treatment. Recent studies have demonstrated that 40 Gy administered in 15 fractions and 34 Gy in 10 fractions were both non-inferior to 60 Gy in 30 fractions in terms of OS (16,17). In addition, 25 Gy in five fractions was shown to be non-inferior to 40 Gy in 15 fractions. Concomitant and adjuvant temozolomide increased the survival benefit of radiotherapy with 40 Gy in 15 fractions (13). The Japan Society for Neuro-Oncology guidelines encourage the consideration of hypofractionated radiotherapy for elderly patients with glioblastoma, adding chemotherapy for patient with good performance (18). However, the optimal dose and fractionation with concomitant temozolomide remain unresolved. This review discusses better management of elderly patients with glioblastoma and highlights future perspectives in caring for this disease population.

Surgical resection

Glioblastoma is characterized by extensive invasion into the surrounding brain parenchyma (19). Such tumor invasion means that surgical resection is unable to provide a cure. Magnetic resonance imaging often demonstrates heterogeneous gadolinium-enhanced lesions with edematous changes to the brain parenchyma. Surgical resection of glioblastoma has been evaluated as the resection rate of gadolinium-enhanced lesions in most clinical studies. Biopsy is adopted in patients with tumors impossible to sufficiently resect due to tumor location or general condition. In retrospective studies of adult glioblastoma, a significant survival advantage was associated with extent of resection (EOR) ≥ 78–98% (20,21). Median OS was 13 months in patients with EOR ≥ 98% and 8.8 months in those with <98% in a study conducted at the University of Texas MD Anderson Cancer Center (20). Median OS was 12.8 months, 13.8 months and 16 months with EOR ≥ 80, ≥ 90 and 100%, respectively, in a study at the University of California (21). In a clinical study assessing the effect of fluorescence-guided resection with 5-aminolevulinic acid, complete resection (CR) of enhanced tumor was higher in patients assigned to receive 5-aminolevulinic acid (65%) compared with those assigned white light (36%) (22). Patients allocated 5-aminolevulinic acid displayed a significantly higher 6-month progression-free survival (PFS) rate (41.0%) than those allocated white light (21.1%) (22). However, no prospective trials have evaluated the contribution of EOR to survival.

In the case of elderly patients with glioblastoma, previous studies have indicated that a safe maximal resection may confer modest survival benefits even for patients >65 years old with glioblastoma (23–28) (Table 1). A randomized study at Helsinki University Hospital indicated that median OS was 5.6 months in 10 patients who underwent craniotomy, longer than the 2.8 months in 13 patients who underwent biopsy (27). The procedure-related complication rate was 10% with craniotomy and 0% with biopsy. In a retrospective study of 342 elderly patients ≥65 years old at the University of Freiburg, surgical resection and stereotactic biopsy were performed in 216 patients (63.2%) and 125 patients (36.5%), respectively (24). Median OS was significantly longer in patients with GTR (10.8 months) compared with partial resection (PR) (8.1 months) or biopsy (3.0 months). A systematic review between 2005 and 2018 demonstrated that total resection was associated with longer postoperative OS (13.13 months) when compared with PR (7.52 months) or biopsy (2.56 months) in seven clinical studies (28). In an Italian cohort of 178 elderly patients, CR was seen in 8 patients (4.5%), GTR in 63 (35.4%), subtotal resection (STR) in 46 (25.8%), PR in 16 (9.0%) and biopsy in 45 (25.3%). Postoperative neurological deficits were found in 11 patients (6.2%), and a worsening of preoperative neurological symptoms was recorded in four patients (2.2%). Tumor location, EOR and postoperative neurological status significantly affected survival (26). The analysis of 18 registries in the Surveillance, Epidemiology and End Results (SEER) program revealed that elderly patients with cerebellar glioblastoma and supratentorial glioblastoma have similar outcomes in OS, and those undergoing maximal resection with adjuvant therapies, independent of tumor location, show improved outcomes (25).

In patients ≥75 years old, analysis of the SEER database demonstrated a similar result that GTR was an independent predictor of OS, cancer-specific survival and early mortality (29). A retrospective review of 82 patients ≥75 years old at the University of Utah found that survival was associated with EOR only for patients without postoperative complications in EOR including no surgery (9.8%), biopsy (22.0%), STR (40.2%) and gross-total resection (23.2%) (30) (Table 1). Twenty-three patients showed 34 postoperative complications and postoperative complications were identified as an independent risk factor for worsened OS (30). Long-term survivors (≥ 12 months) and short-term survivors (< 12 months) had similar median preoperative KPS, but long-term survivors showed no deterioration in postoperative KPS and no postoperative complications (30). Although no randomized studies have provided strong evidence to evaluate the benefits of surgical resection in elderly patients with newly diagnosed glioblastoma, the existing literature recommends maximal safe resection to prolong OS in elderly patients with good preoperative condition if postoperative complications can be avoided. Surgical indications should be defined based on preoperative performance status instead of biological age.

Radiotherapy

Radiotherapy shows potential as the main postoperative treatment for patients with glioblastoma. Early studies reported that radiotherapy had a significant influence on the survival of patients with malignant glioma in a dose-effect manner (31–33). In a retrospective study conducted at the University of Tokyo, median OS in patients with glioblastoma was 16.2 months with 80–90 Gy and 12.4 months with 60 Gy, but OS did not differ between 80 Gy and 90 Gy. A higher frequency of radiation-induced white matter abnormalities was identified with 80–90 Gy, without incurring increased disability (33). A randomized controlled study by the Medical Research Council Brain Tumor Working Party revealed that 60 Gy in 30 fractions prolonged

Table 1. Outcomes of surgical treatment in elderly patients with glioblastoma

Authors, publication year, study design	Diagnosis	Age cut-off, years	Intervention	Number	Adjuvant therapy	mOS, months
Vuorinen et al. 2003 (27)	Grade IV glioma (83%)	≥65	Stereotactic biopsy	13	Radiotherapy (16–60 Gy)	2.8
Prospective	Grade III glioma (17%)		Open craniotomy and resection	10		5.6
Heiland et al. 2018 (24)	GBM	≥65	Gross total resection	142	Stupp 44, RTa 27, TMZa 58	10.8
Retrospective			Partial resection	75	Stupp 26, RTa 15, TMZa 20	8.1
			Biopsy	125	Stupp 29, RTa 18, TMZa 45	3
Cunha et al. 2019 (28)	GBM	≥65	Total resection	473	N/A	13.13
Systematic review			Partial resection	513	N/A	7.52
			Biopsy	90	N/A	2.56
Pessina et al. 2018 (26)	GBM	≥65	Complete resection	8	RT 178, concomitant TMZ 149, adjuvant TMZ 132	24.5
Retrospective			Gross total resection	63		15.1
			Subtotal resection	46		11.9
			Partial resection	16		8
			Biopsy	45		8.1
Karsy et al. 2018 (30)	GBM	>75	Gross total resection	19	None 17, TMZ 22, RT 32, bevacizumab 7, other 4	12.1
Retrospective			Subtotal resection	33		5
			Biopsy	18		3.7
			No surgery	8		0.8

mOS: median overall survival; fr: fractions; GBM: glioblatoma; N/A: not available, Stupp; Stupp regimen, RTa; radiotherapy alone, TMZa; temozolomide alone, RT; radiotherapy, TMZ; temozolomide

OS (12 months) compared with 45 Gy in 20 fractions (9 months) (34). As doses exceeding 60 Gy increased morbidity in some studies, 60 Gy in 30 fractions has been selected in most trials for glioblastoma (35).

The disadvantages of 60 Gy in 30 fractions are a prolonged initial treatment period, which is often associated with longer hospitalization, and deterioration of quality of life (QOL) due to radiation-induced brain damage (15). Reducing the burden of treatment while maintaining efficacy is important for elderly patients with glioblastoma, which shows poor prognosis (15). Hypofractionated radiotherapy has thus been evaluated in the elderly population. Three other phase III trials were conducted for further hypofractionated radiotherapy in elderly patients with newly diagnosed glioblastoma. Those studies compared 40 Gy in 15 fractions versus 60 Gy in 30 fractions (16), 34 Gy in 10 fractions versus 60 Gy in 30 fractions (17) and 40 Gy in 15 fractions versus 25 Gy in 5 fractions (36,37), finding non-inferior results in terms of safety or efficacy for elderly patients with newly diagnosed glioblastoma (Table 2) (13,16,17,36,38,39). According to these results, radiotherapeutic regimens of 45 Gy in 20 fractions, 40 Gy in 15 fractions, 34 Gy in 10 fractions and 25 Gy in 5 fractions have been considered to offer similar efficacy and safety for elderly patients with glioblastoma (16,17,36,37). However, all those studies comprised small sample sizes and the results have not been confirmed by other investigations, so the optimal dose and number of fractions remain unclear (15).

An analysis of the United States National Cancer Database between 2005 and 2012 showed that utilization of hypofractionated radiotherapy increased from 7% to 19% during this period in 9556 patients ≥65 years old with glioblastoma, suggesting that hypofractionated radiotherapy may offer better treatment than best supportive care alone and as good as conventional radiotherapy alone (40). In a review of patients ≥65 years old with glioblastoma in the National Cancer Data Base between 2006 and 2012, 126 patients (2.5%) underwent hypofractionated radiotherapy, whereas 5000 (97.5%) received conventional radiotherapy. Patients who underwent hypofractionated radiotherapy were older, showed worse performance status, underwent biopsy only and were more likely to receive treatment at an academic facility. Conventional radiotherapy was associated with improved median OS (10.7 vs. 6.2 months) (41). According to a UK investigation into the management of elderly patients with glioblastoma between 2016 and 2017, median OS was 5.0 months. Approximately 31.9% of patients received combined chemoradiation (42).

Retrospective studies have also demonstrated survival benefits of hypofractionated radiotherapy combined with temozolomide or temozolomide plus bevacizumab (43,44). A phase II study of 52.5 Gy in 15 fractions for elderly patients with poor conditions including age ≥ 70 years and KPS score ≤ 60 showed that median PFS and OS were 5.0 months and 8.0 months, respectively. KPS = 60, recursive partitioning analysis class V, methylated hypermethylation of *MGMT* promoter, stable neurological status or improvement after surgery, and hypofractionated radiotherapy with concurrent and adjuvant temozolomide were associated with better outcomes (45). In the interim results of a phase II study to evaluate 34 Gy in 10 fractions with temozolomide in patients ≥70 years old with glioblastoma, median PFS and OS were 6 months and not reached on a median follow-up of 9 months, respectively (46). In 2017, the CE.6 trial demonstrated that median OS was longer with radiotherapy comprising 40 Gy in 15 fractions plus concomitant and adjuvant temozolomide (9.3 months) than with 40 Gy in 15 fractions alone

Table 2. Randomized controlled trials in elderly patients with glioblastoma

Authors, publication year, study name	Diagnosis	Age cut-off, years	Number	Intervention	mPFS, months	mOS, months
Bleehen et al. 1991 (34)	Astrocytoma		156 (49 ≥ 60 years)	45 Gy/20 fr	N/A	9 (N/A ≥ 60 years)
Medical Research Council trial	WHO Grade 3 (33%), 3 + 4 (5%), 4 (61%)		318 (91 ≥ 60 years)	60 Gy/30 fr	N/A	12 (N/A ≥ 60 years)
Roa et al. 2004 (16)	GBM	≥60	47	60 Gy/30 fr	N/A	5.1
			48	40 Gy/15 fr	N/A	5.6
Keime-Guibert et al. 2007 (38)	AA (2%), GBM (96%)	≥70	42	Best supportive care	1.2	3.9
ANOCEF			39	50 Gy/28 fr	3.4	6.7
Wick et al. 2012 (39)	AA (11%), GBM (89%)	>65	178	60 Gy/30 fr	4.7	9.6
NOA-08			195	Dose-dense temozolomide	3.3	8.6
Malmström et al. 2012 (17)	GBM	>70	100	60 Gy/30 fr	N/A	6
Nordic study			98	34 Gy/10 fr	N/A	7.5
			93	Temozolomide	N/A	8.3
Roa et al. 2015 (36)	GBM	≥65	50	40 Gy/15 fr	4.2	6.4
			48	25 Gy/5 fr	4.2	7.9
Perry et al. 2017 (13)	GBM	≥65	281	40 Gy/15 fr	3.9	7.6
CE.6			281	40 Gy/15 fr + temozolomide	5.3	9.3
Wirsching et al. 2018 (61)	GBM	≥65	50	40 Gy/15 fr + bevacizumab	7.6	12.1
ARTE trial			25	40 Gy/15 fr	4.8	12.2

mPFS: median progression-free survival; mOS: median overall survival; fr: fractions; N/A: not available; GBM: glioblatoma

in elderly patients ≥65 years old with newly diagnosed glioblastoma (13). However, a select group of elderly patients with excellent performance status and hypermethylation of *MGMT* promoter or GTR may experience favorable survival with the Stupp regimen (47). The optimal dose and number of fractions thus remain unclear when administered in combination with temozolomide (15).

Chemotherapy

Temozolomide, an oral alkylating agent, exerts antitumor activity as a single agent against malignant glioma (48). The CE.3 trial demonstrated that a regimen of concomitant and adjuvant temozolomide with radiotherapy (Stupp regimen) significantly improved median OS from 12.1 to 14.6 months compared with radiotherapy alone in patients with glioblastoma younger than 70 years old (7,8). However, subgroup analysis of the CE.3 trial revealed a diminishing benefit from the addition of temozolomide with increasing age (hazard ratio 0.80 for 66–70 years) (49). Studies exploring the Stupp regimen in elderly patients with glioblastoma have demonstrated benefits compared with radiotherapy alone, although high frequencies of toxicities such as mental status deterioration and leukoencephalopathy were identified (5,10,50). Good performance status and hypermethylation of *MGMT* promoter were associated with favorable prognosis from the Stupp regimen in the elderly population. Temozolomide seemed to have minimal impact on seizure control in elderly patients with glioblastoma (51).

The Nordic study demonstrated that temozolomide (200 mg/m^2 on Days 1–5 of every 28 days for up to 6 cycles) prolonged median OS from 6.0 months to 8.3 months compared with conventional radiotherapy 60 Gy in 30 fractions (17). In the temozolomide group, patients with hypermethylation of the *MGMT* promoter displayed significantly longer survival (9.7 months) than those with hypomethylation of the *MGMT* promoter (6.8 months). The most common grade 3–4 adverse events in the temozolomide group were neutropenia (12%) and thrombocytopenia (21%). The NOA-08 trial demonstrated that the regimen of dose-dense temozolomide (100 mg/m^2, given on days 1–7 of a 1 week on, 1 week off cycle) alone is non-inferior to radiotherapy at 54–60 Gy in 30 fractions among elderly patients with anaplastic astrocytoma or glioblastoma and age > 65 years (39). Grade 3–4 adverse events in the temozolomide group were neutropenia (8.2%), lymphocytopenia (23.6%), thrombocytopenia (7.2%), increased liver-enzyme concentrations (15.4%) and thromboembolic events (12.3%). A long-term update of NOA-08 revealed that median OS was 8.2 months in the temozolomide group versus 9.4 months in the radiotherapy group (52). In patients with *MGMT* methylated tumors, dose-dense temozolomide improved OS from 9.6 to 18.4 months compared with radiotherapy. Pooled analysis of trials controlling for *MGMT* promoter methylation status demonstrated that temozolomide monotherapy confers similar survival benefits to radiotherapy in combination with temozolomide (53).

The CE.6 trial demonstrated that a regimen of concomitant and adjuvant temozolomide significantly improved median OS from 7.6 to 9.3 months compared with radiotherapy alone in patients ≥65 years old with glioblastoma (13). Addition of temozolomide did not decrease QOL and temozolomide-related adverse events were manageable. Subgroup analysis of the CE.6 trial revealed that patients 65–70 years old displayed less benefit from temozolomide than those 71–75 years old or ≥ 76 years old. As presumptive reasons, fewer patients 65–70 years old than 71–75 years old are enrolled and patients 65–70 years old with good performance status are generally treated with the Stupp regimen. Based on these considerations, a regimen of radiotherapy as 40 Gy in 15 fractions plus temozolomide could represent an appropriate standard

treatment for patients ≥71 years old with newly diagnosed glioblastoma (15). Using 14 studies of 4561 patients, a network-based analysis demonstrated that the Stupp regimen provided similar survival benefit to hypofractionated radiotherapy in combination with temozolomide or hypofractionated radiotherapy alone. Recent meta-analyses and systematic reviews have demonstrated that hypofractionated radiotherapy in combination with temozolomide achieved the highest probability of improving survival in older patients with glioblastoma followed by the Stupp regimen (53–57).

Bevacizumab is a humanized monoclonal antibody targeting the vascular endothelial growth factor (VEGF)-A ligand, which inhibits vascular endothelial cell proliferation and angiogenesis (58). Bevacizumab improved PFS, but not OS in patients with newly diagnosed glioblastoma (59,60). The Avastin Plus Radiotherapy in Elderly Patients With Glioblastoma (ARTE) trial demonstrated that the addition of bevacizumab to hypofractionated radiotherapy of 40 Gy in 15 fractions did not prolong OS in 75 elderly patients ≥65 years old (bevacizumab + radiotherapy: 12.1 months; radiotherapy alone: 12.2 months) (61). Adding molecular subtypes into that model identified an association of the RTK II gene methylation subtype with inferior OS. The ANOCEF Phase II Trial suggested that the addition of bevacizumab to temozolomide is active in 66 elderly patients ≥70 years old with glioblastoma with KPS score < 70 with acceptable tolerance (62). Median PFS and OS were 15.3 weeks and 23.9 weeks, respectively. A retrospective study of SEER-Medicare data for patients ≥66 years old between 2006 and 2011 demonstrated that bevacizumab treatment was associated with lower risk of death, suggesting potential benefits of bevacizumab among elderly patients with glioblastoma (63).

Managements of recurrence

No standard treatment has been defined for glioblastoma recurrence, but re-resection, re-irradiation and systemic chemotherapy with bevacizumab or other drugs are selectable options according to patient status, particularly in elderly patients. The majority of glioblastomas in elderly patients recur within 6 months after the initial multimodal therapy (13,17,39), which is a shorter period than in younger patients. An analysis of the SEER-Medicare database reported low re-resection rates, with no survival advantage for those elderly patients who did undergo re-resection (64). Some retrospective studies have demonstrated that elderly patients with recurrent glioblastoma showed a survival benefit from re-resection (65,66). Re-irradiation in elderly patients with glioblastoma was feasible with acceptable safety, offering a possible treatment option. Patients with longer intervals from first-line treatment and patients who received systemic treatments in addition to re-irradiation showed better prognosis (67). In a retrospective study, the efficacy and safety of bevacizumab in recurrent glioblastoma appear similar in elderly and non-elderly patients. However, the clinical benefit seemed less evident in younger patients (68).

Prognostic markers

Performance status is a key prognostic factor to be considered for management decisions in elderly patients with newly diagnosed glioblastoma (69). Retrospective studies identified predictors for poor OS of older age, lower KPS, white people, higher comorbidity score, worse socioeconomic status, community treatment, tumor multifocality, STR, aphasia after surgery, motor dysfunction after surgery and no adjuvant treatment (30,69–74). A Fine-Gray competing risk model of 4975 elderly patients ≥65 years old with glioblastoma from the SEER database demonstrated age ≥ 75 years old, white people, size >5.4 cm, frontal lobe tumor and overlapping lesion were independently associated with more glioblastoma-related death, whereas GTR, chemotherapy and chemoradiation were identified as independently protective factors for glioblastoma-related death (75). In a secondary analysis of the CCTG CE.6 trial evaluating the impact of lymphopenia, development of lymphopenia was not associated with radiotherapy alone, but baseline lymphopenia was associated with worsened OS (76). Multiple socioeconomic parameters can influence access to treatment modalities for elderly patients compared with younger patients in different geographic regions of the United States (77).

The Cumulative Illness Rating Scale (CIRS) is a comprehensive and reliable instrument for assessing physical impairment (78). As high CIRS plays a predictive role for OS in elderly patients with glioblastoma (79), if the prognostic role of comorbidity measured by CIRS on outcome can be confirmed, CIRS offers an interesting scale for optimal treatment according to personal comorbidities. The predictive value of the comprehensive geriatric assessment (CGA) regarding tolerance of chemotherapy and prediction of early mortality was validated for elderly patients with glioblastoma in a retrospective trial (80,81). CGA score offered a good predictor of OS in elderly patients with glioblastoma, which may prove useful in making treatment decisions.

Analyses of the CGGA and TCGA databases detected no age-related hallmarks of glioblastoma including pathological characteristics or mutations (82). However, isocitrate dehydrogenase 1 (*IDH1*) mutation is rare in the elderly, and more often identified for glioma in young populations (17,83). Glioblastomas in elderly patients possess unique molecular signatures such as telomerase reverse transcriptase promoter mutation, *PTEN* mutation/deletion, *MGMT* methylation, high expression of *VEGF-A*, hypermethylation in polycomb group protein target genes, upregulation of angiogenesis-related genes, somatic copy number alterations and *CDK4/MDM2* coamplification (84–89) (Table 3). The genetic analysis in the NOA-08 trial demonstrated an age-independent and stable frequency of *MGMT* promoter hypermethylation (83). DNA methylation-based classification has recently become a useful tool to classify brain tumors (90). The characterization of molecular subgroups revealed three types of IDH wildtype glioblastoma, indicating subgroups of receptor tyrosine kinase I (RTK I), receptor tyrosine kinase II (RTK II) and mesenchymal. In the NOA-08 trial, *MGMT* promoter methylation is a strongly predictive biomarker for the choice between radiotherapy and temozolomide. This indicates favorable long-term outcomes with initial temozolomide monotherapy in patients with *MGMT* promoter-methylated tumors, primarily in the RTK II subgroup (52). Investigation of the DNA methylome (Human Methylation 450 K BeadChip) for age-related associations revealed that acceleration of DNA methylation with age was significantly associated with better outcomes (91). These molecular characteristics provide the possibility of developing age-specific adjuvant treatments.

Future perspectives

No strong evidence is yet available to establish a 'best' regimen for elderly populations with glioblastoma. The goal of treatment in elderly patients with glioblastoma and good performance status is to extend OS preserving KPS, QOL and cognitive function,

Table 3. Genetic signature of glioblastoma associated with prognosis in elderly patients

Authors, publication year	Genetic signature	Possible impact on prognosis
Bozdag et al. 2013 (85)	Hypermethylation in polycomb group protein target genes	Poor
Nghiemphu et al. 2009 (84) Bozdag et al. 2013 (85)	Upregulation of VEGF-A, angiogenesis-related genes	Poor
Ferguson et al. 2016 (87) Fukai et al., 2020 (89)	PTEN mutation/deletion	Poor
Wiestler et al. 2013 (83) Ferguson et al. 2016 (87)	IDH1/2 mutation	Good
Wiestler et al. 2013 (83)	MGMT promoter hypomethylation	Poor
Eckel-Passow et al. 2015 (86)	TERT promoter mutation	Poor
Cimino et al. 2018 (88) Fukai et al. 2020 (89)	CDK4/MDM2 coamplification CDK4 amplification/gain	Poor
Bady et al. 2022 (91)	DNA methylation age acceleration	Good

Table 4. Biologically effective dose as estimated by the LQ model

		α/β value			
Authors, publication year	Radiation dose/fractions	1.2	3.0	5.6	10.0
Conventional radiotherapy	60 Gy/30 fr	60.0	60.0	60.0	60.0
Bleehen et al. 1991 (34)	45 Gy/20 fr	48.5	47.3	46.5	45.9
Perry et al. 2017 (13)	40 Gy/15 fr	48.4	45.4	43.6	42.3
Roa et al. 2015 (36)	25 Gy/5 fr	48.4	40.0	34.9	31.3
Malmström et al. 2012 (17)	34 Gy/10 fr	48.9	43.5	40.3	38.0
Perlow et al. 2022[a] (105)	52.5 Gy/15 fr	77.1	68.3	62.9	59.1

[a]A retrospective study of 66 patients

which is the same in younger patients. In elderly patients with poor performance status, however, the optimal endpoint is considered to improve or preserve their condition. A web-based survey showed that treatment recommendations for elderly patients with newly diagnosed glioblastoma vary widely (92). Statistical comparisons have demonstrated that the common treatment regimens for elderly patients with glioblastoma in previous randomized controlled trials conferred similar survival benefits. Adjustments for the methylation status of *MGMT* promoter demonstrated that radiotherapy alone was inferior to temozolomide-based treatments (53). A randomized study comparing temozolomide monotherapy with radiotherapy combined with temozolomide is warranted. As a framework for modeling COVID-19 risk on the analysis of five randomized trials, hypofractionated radiotherapy with concurrent and adjuvant temozolomide demonstrated the best outcomes in low- and medium-risk scenarios during the COVID-19 pandemic (93).

Tumor-treating fields represent a locoregional, noninvasive, antimitotic therapy delivering low-intensity, intermediate-frequency alternating electric fields to the tumor. Combining tumor-treating fields (200 kHz) with maintenance temozolomide significantly improved PFS and OS in elderly patients with newly diagnosed glioblastoma in the EF-14 trial, without significantly increasing systemic toxicity or negatively affecting QOL. Tumor-treating fields correlated with low-grade, manageable skin adverse events (94–98). Tumor-treating fields offer an option for elderly patients with good performance status.

A systematic review and network meta-analysis (NMA) also showed that OS estimates from NMA did not provide strong evidence of a difference between different hypofractionated radiotherapies of 40 Gy versus 45 Gy; 34 Gy versus 45 Gy; 25 Gy versus 45 Gy; 34 Gy versus 40 Gy and 25 Gy versus 34 Gy (99). A multi-institutional retrospective study in Korea reported that conventional radiotherapy significantly improved OS compared with short-course radiotherapy in selected elderly patients amenable to chemoradiation (100).

Although concomitant and adjuvant temozolomide is effective in addition to hypofractionated radiotherapy comprising 40 Gy in 15 fractions, one clinical question is which radiation dose fractionation can provide the most survival benefit, particularly in combination with temozolomide, for elderly patients with newly diagnosed glioblastoma.

In August 2020, the Brain Tumor Study Group and Radiation Therapy Study Group of the Japan Clinical Oncology Group (JCOG) started a multi-institutional randomized phase III trial to confirm the non-inferiority of radiotherapy at 25 Gy in 5 fractions with concomitant (150 mg/m^2/day, 5 days) and adjuvant temozolomide >40 Gy in 15 fractions with concomitant (75 mg/m^2/day, every day from first to last day of radiation) and adjuvant temozolomide in terms of OS for elderly patients with newly diagnosed glioblastoma (JCOG1910, AgedGlio-PIII) (15). The results of JCOG1910 will confirm whether hypofractionated radiotherapy requiring a shorter treatment period with temozolomide can overcome the disadvantages of standard treatment without compromising efficacy (15). If the primary endpoint in JCOG1910 is met, radiotherapy at 25 Gy in five fractions with concomitant and adjuvant temozolomide will be established as a standard of care for elderly patients with newly diagnosed glioblastoma.

On the linear-quadratic (LQ) model, equivalent-dose fractionation can be estimated by calculating equivalent doses in 2-Gy fractions (101). Previous analyses have indicated that the α/β values of glioma and normal brain tissue were 5–10 Gy and 2–3 Gy, respectively (102–104). However, the results of phase III trials have suggested that the α/β value of glioblastoma in elderly patients is estimated as <1.2 Gy (13,17,36) (Table 4). Retrospective analysis of elderly patients ≥65 years old who received resection and hypofractionated radiation with temozolomide demonstrated that 52.5 Gy in

15 fractions was associated with superior OS compared with 40 Gy in 15 fractions (105). If JCOG1910 demonstrates the non-inferiority of radiotherapy of 25 Gy in 5 fractions over 40 Gy in 15 fractions on addition of temozolomide, the α/β value of glioblastoma in elderly patients will be estimated as <1.2 Gy.

Conclusions

The survival impacts of multimodal treatment differ among elderly patients with impaired performance status, advanced age, severe comorbidities and hypomethylation status of *MGMT* promoter. Biological age is more important than chronological age. Chronological age should not prohibit multimodal treatment. Instead, optimal management should be considered for the condition of each individual patient to reduce complications and achieve satisfactory QOL. Although hypofractionated radiotherapy in combination with temozolomide following surgery has become the recommended treatment for elderly patients with glioblastoma, several issues remain unresolved. The optimal dose and number of fractions in radiotherapy, particularly in combination with temozolomide, should be explored for better survival and QOL.

Availability of data and materials

Data sharing is not applicable for this article, as no datasets have been generated or analyzed at the time of submission.

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Contributions

Y.A. wrote the manuscript. All authors critically revised the manuscript for intellectual content and approved the final manuscript.

Consent for publication

Not applicable.

Competing interests

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