



Management of glioblastoma in the elderly

Idoia Morilla^{1,2,3} · Edinson Caviedes⁴ · Regina Gironés Sarrió⁵ · Borja López de San Vicente Hernández⁶ · Natalia Luque Caro⁷ · Sonia del Barco⁸ · Juana M. Cano⁹ · María Ángeles Vaz-Salgado¹⁰

Received: 9 June 2026 / Accepted: 6 August 2026
© The Author(s) 2026

Abstract

Glioblastoma is the most aggressive and common malignant primary brain tumor among adults. Due to its aggressiveness, GBM entails a short median overall survival and fatal outcomes. Incidence notably increases with age, 50% of patients being diagnosed at the age of 65 or older. Given that cognitive loss is commonly confused with age-related cognitive impairment, delays in diagnosis are frequent. Furthermore, the elderly are a vulnerable group, commonly having poorer functional status, more comorbidities, and reduced tolerance to intensive treatments. Therefore, clinical and therapeutic implications should be considered within a multidisciplinary approach. The aim of the present study was to review the current knowledge on the management of glioblastoma in the elderly population (≥ 65 years).

Keywords Glioblastoma · Older adults · Geriatric oncology · MGMT · Temozolomide · Radiotherapy · Surgery

Introduction

Glioblastoma (GBM) is the most frequent malignant primary tumor of the central nervous system (CNS), accounting for 48.6% of total CNS malignancies [1]. In the 5th edition

of the World Health Organization (WHO) Classification of Tumors of the Central Nervous System (CNS) (2021), the adult entity is defined as 'glioblastoma, IDH-wildtype', CNS WHO grade 4. Grade 4 may be assigned by classic histology (necrosis and/or microvascular proliferation) and

✉ Idoia Morilla
idoiamorilla@gmail.com

Edinson Caviedes
edicasan@gmail.com

Regina Gironés Sarrió
girones_reg@gva.es

Borja López de San Vicente Hernández
borjalsv@gmail.com

Natalia Luque Caro
nluquecilla@gmail.com

Sonia del Barco
sdelbarco@iconcologia.net

Juana M. Cano
juanamariacano@gmail.com

María Ángeles Vaz-Salgado
mariaangeles.vaz@salud.madrid.org

¹ Medical Oncology Department, Hospital Universitario de Navarra (HUN), Irunlarrea 3, 31008 Pamplona, Spain

² Oncobiona Group, Navarrabiomed-Instituto de Investigación Sanitaria de Navarra (IdiSNA), Irunlarrea 3, 31008 Pamplona, Spain

³ Departamento de Ciencias de Salud, Universidad Pública de Navarra (UPNA), Campus de Ciencias de la Salud - Universidad Pública de Navarra (UPNA). Avenida de Barañain s/n, 31008 Pamplona, Spain

⁴ Servicio de Oncología Médica, Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Madrid, Spain

⁵ Servicio de Oncología Médica, Hospital Universitari i Politècnic La Fe, Valencia, Spain

⁶ Oncología Médica, Hospital Universitario Basurto, Bilbao, Spain

⁷ Servicio de Oncología Médica, Hospital Universitario Virgen de las Nieves, Granada, Spain

⁸ Servicio de Oncología Médica, Instituto Catalán de Oncología (ICO), Hospital Universitario Josep Trueta, Girona, Spain

⁹ Servicio de Oncología Médica, Hospital General Universitario de Ciudad Real, Ciudad Real, Spain

¹⁰ Servicio de Oncología Médica, Hospital Universitario Ramón y Cajal, Madrid, Spain

can also be supported by specific molecular features such as *TERT* promoter mutation, *EGFR* amplification, and/or combined whole-chromosome 7 gain with chromosome 10 loss (+7/−10). GBM is fast-growing, cytologically malignant, and typically associated with rapid pre- and postoperative disease evolution [2]. It translates into a short median overall survival (OS) of around 15 months [1]. Its incidence notably increases with age, and around 50% of patients with GBM are diagnosed at the age of ≥ 65 . The elderly are a highly heterogeneous group. Some patients remain functionally independent and can tolerate multimodal treatment, whereas others present with poorer functional status, more comorbidities, and reduced tolerance to intensive treatments. These factors may influence treatment eligibility and survival. Moreover, older patients have historically been under-represented in clinical trials, limiting the generalizability of conventional treatment recommendations to frail and very old populations.

Therefore, it entails specific diagnostic, clinical and therapeutic decisions that require a multidisciplinary approach [3].

The main symptoms of GBM include headache, nausea, vomiting and cognitive abnormalities (confusion and memory loss), personality changes, epileptic seizures, focal neurological deficits, and balance or coordination disorders, although it can also be asymptomatic [4]. Among older adults, the initial presentation may be particularly subtle. Cognitive decline, apathy, confusion, reduced mobility, falls, or loss of independence may be incorrectly attributed to normal aging, dementia, cerebrovascular disease, depression, or medication-related effects. These overlapping manifestations can delay new diagnosis, allowing further neurological and functional deterioration before treatment is initiated [5]. Hence, it is of paramount importance to perform a comprehensive anamnesis and a thorough neurological exam in this group age.

Diagnosis

Contrast-enhanced brain magnetic resonance imaging (MRI) is the imaging modality of choice for the initial evaluation of suspected GBM [6]. An integrated histopathological and molecular evaluation is essential for accurate classification, prognostic stratification and treatment selection. Besides molecular biomarkers relevant for prognosis have been identified:

- *IDH1/IDH2*: mutations in the genes encoding for isocitrate dehydrogenase (IDH) associate with better prognosis, although these are rare in people > 40 years old [7].
- *O⁶-methylguanine-DNA-methyltransferase (MGMT) gene*: Is the most clinically relevant predictive molecular biomarker for treatment selection in older patients

with GBM [8]. It is associated with increased sensitivity to temozolomide (TMZ) and predicts a greater survival benefit from TMZ-containing treatment. Its clinical relevance is particularly pronounced in this population.

- *EGFR*: gene amplification is commonly observed in the elderly, and it associates a worse prognosis. It may also indicate a potential benefit to targeted therapies [9].
- *TERT*: mutations in the *TERT* promoter and whole-chromosome copy-number changes, such as chromosome 7 gain and chromosome 10 loss (+7/−10), together with *EGFR* amplification, are among the molecular alterations that can support the diagnosis of glioblastoma, IDH-wildtype, in the absence of classic histopathological features, within the WHO 2021 framework [2].

Management

Surgical management is one of the cornerstones of GBM treatment. The main objective of surgical management is to achieve the maximum extent of resection (EOR) without causing unacceptable neurological deficits. Diagnostic confirmation requires tissue sampling via stereotactic biopsy or, preferably, surgical resection [10]. The choice largely depends on the patient's functional status, with a Karnofsky Performance Status (KPS) score ≥ 70 being a criterion for greater benefit with resection. In frail patients or those with significant comorbidities, biopsy is usually preferable to minimize risks [11]. Frailty is a clinically state of increased vulnerability resulting from aging-associated decline in physiological reserve, which compromises the ability to respond to stressors. It is defined by meeting three out of five criteria: low grip strength, low energy, slowed waking speed, low physical activity, and/or unintentional weight loss [12]. It is identified and quantified through comprehensive geriatric assessment (CGA). Patients aged ≥ 70 years should undergo frailty screening using the G8 questionnaire. Those with an abnormal G8 score (≤ 14), or with clinically evident vulnerabilities despite a normal score, should be referred for a CGA. This assessment should evaluate functional status, cognitive function, comorbidities, polypharmacy, nutritional status, mood, mobility and risk of falls, and social support. In the glioblastoma-specific study by Lombardi et al., GCA included the Cumulative Illness Rating Scale (CIRS), Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL), Mini-Mental State Examination (MMSE), and Geriatric Depression Scale (GDS), and provided prognostic information independently of KPS [13].

It is essential to adopt a multidisciplinary approach, adapting the intensity of treatment to the patient's baseline situation and personal preferences. The priority is not only to prolong survival, but also to preserve quality of life (QoL) [14]. Treatment options include surgery when feasible, tailored radio-chemotherapy regimens, chemotherapy alone,

or best supportive care, guided by age, performance status, MGMT promoter methylation status, and the patient's overall geriatric fitness [15].

Surgical management of glioblastoma in people of advanced age

The type of surgical intervention, together with age and functional status, are key prognostic factors. In contemporary series, the median survival reaches 8.5 months in patients < 75.5 years of age, in good general health and undergoing partial or complete resection, compared to 3.1 months in those undergoing biopsy alone and with a KPS score < 70 [16].

Although age is not a contraindication factor for GBM surgery, data on surgical resection with biopsy in people of advanced age are heterogeneous. The sole randomized clinical trial in this setting, the ANOCEF study, compared the survival in patients ≥ 70 years old with a KPS score of ≥ 50 and presenting with a radiological suspicion of operable GBM tumoral who underwent resection versus those who underwent biopsy. This study did not find a significant benefit in terms of OS between the surgery and the biopsy (9.37 and 8.96 months, respectively). However, the surgery group had an increased progression-free survival (PFS) (5.06 vs. 4.02 months, $p = 0.034$) and less deterioration of the QoL, without an increase in the morbidity and mortality [17].

In contrast, several retrospective studies demonstrated a positive impact of surgery on OS, being the EOR a key prognostic factor. One German study including population aged > 65 years or older with GBM investigated the functional and oncological outcome of surgical treatment comparing gross total resection (GTR), partial resection (PR), and stereotactic biopsy. The median OS was significantly higher in patients who underwent GTR (10.8 months) compared to those with PR (8.1 months), and biopsy (3 months). Additionally, higher preoperative KPS was associated with improved OS [18].

Similarly, another study carried out in Austria showed that OS differed significantly between EOR groups: 4 months after biopsy, 8.3 months after subtotal resection, and 13.8 months after GTR [19].

People of advanced age may suffer perioperative complications and mortality after surgery. The Swedish Brain Tumor Registry included patients aged 65 years or older who underwent surgery for GBM. The registry reported a low postoperative morbidity rate of 24%, with factors such as resection and not having a multifocal tumor being associated with a higher risk of postoperative morbidity. More aggressive surgeries performed on potentially resectable tumors are associated with a higher rate of complications; hence, patient selection becomes particularly important. The postoperative

mortality rate was 5%, which was associated with increased age, biopsy, and poor performance status [20]. Overall, these findings support surgery as a feasible alternative in patients of advanced age with GBM, if the indication is based on careful selection considering KPS, comorbidities, tumor characteristics, and patient's preferences.

Adjuvant treatment in elderly patients with glioblastoma

Radiotherapy (RT) combined with supportive care has long been an essential treatment option in the management of elderly patients with GBM. Keime-Guibert et al. were the first to demonstrate that RT reports clear benefit on survival, even in patients 70 years of age or older. This study compared the median survival of patients ≥ 70 years with a newly diagnosed GBM and a KPS of ≥ 70 . Patients who received RT plus supportive care had a median survival of 29.1 weeks, compared to just 16.9 weeks for the patients who received supportive care alone [5]. In 2004, Roa et al. explored the possibility of shortening the course of RT. They compared standard RT (60 Gy in 30 fractions over 6 weeks) with a course of RT (40 Gy in 15 fractions over 3 weeks). The OS were comparable for both treatments (5.1 months for standard RT vs 5.6 months for the shorter course). However, the shorter course involved a significantly lower therapeutic load [21]. These findings prompted the use of hypofractionated regimens in elderly and fragile patients. In 2012, the Nordic trial further strengthened this trend. It included 300 patients > 60 years, who were randomized to receive TMZ in monotherapy, hypofractionated RT (34 Gy administered in 3.4 Gy fractions over 2 weeks), or standard RT (60.0 Gy administered in 2.0 Gy fractions over 6 weeks). For patients older than 70 years, OS was better with TMZ and with hypofractionated RT than with standard RT. Additionally, hypofractionated RT was associated with better tolerance, making it a particularly attractive strategy in elderly patients [22]. It should be highlighted that, in addition to efficacy, the impact of RT on cognitive function and QoL plays a decisive role in decision-making. Additional evidence supports further treatment de-intensification for frail patients: an International Atomic Energy Agency randomized phase III trial compared 25 Gy in 5 fractions (1 week) versus 40 Gy in 15 fractions (3 weeks) in elderly and/or frail patients with newly diagnosed GBM, reporting non-inferior outcomes for the shorter regimen, which can be considered when functional status or logistics preclude longer schedules [23].

The introduction of TMZ marked a significant advancement in the management of GBM. In elderly patients, the use of TMZ is strongly linked to the methylation status of the *MGMT* gene promoter, the main predictive biomarker available. The NOA-08 trial included patients aged $\geq$

65 years and compared standard RT with TMZ administered as an alternating regimen. The study demonstrated the non-inferiority of chemotherapy, with similar OS in both arms (9.6 vs. 8.6 months). The most interesting finding was the analysis according to *MGMT* methylation status. It revealed that patients with methylated promoter clearly benefited from TMZ treatment (Event Free Survival (EFS) 8.4 vs. 4.6 months), while in patients with non-methylated *MGMT* promoter, RT offered better results [15]. Similarly, the Nordic trial reached comparable conclusions: TMZ alone was particularly effective in elderly patients with a methylated *MGMT* promoter when compared to patients with non-methylated *MGMT* promoter (OS 9.7 vs. 6.8 months) [22]. Taken together, these trials established the determination of *MGMT* status as a crucial step before prescribing chemotherapy in this population.

In patients younger than 70 years old, it was established the Stupp protocol (RT 60 Gy + concomitant-adjuvant TMZ) [10] as the best regimen. However, no confirmatory studies in the elderly were available.

The role combining RT and temozolomide in older patients was clarified by the phase III trial [24]. It included 562 patients ≥ 65 years with newly diagnosed GBM, who were randomly assigned to receive either hypofractionated RT alone (40 Gy in 15 fractions) or RT with concomitant TMZ. Patients on RT + TMZ showed a significantly longer OS than with RT alone (9.3 months vs. 7.6 months) and longer median PFS (5.3 months vs. 3.9 months) vs RT alone. Among patients with a methylated *MGMT* promoter status, the median OS was 13.5 months with RT+TMZ and 7.7 months with RT alone, while patients with unmethylated *MGMT* status showed only limited benefit [24]. These findings support the use of *MGMT* promoter methylation status to guide treatment selection. However, therapeutic decisions should not be based on chronological age alone, but should also consider performance status, frailty, comorbidities, cognitive function, and patient preferences [13, 25–29]. Beyond large clinical trials, a range of prospective and retrospective studies support the effectiveness of chemoradiotherapy in elderly patients. For instance, Brandes et al. conducted a prospective trial in elderly patients with GBM and they found that patients treated with RT+TMZ reached an OS higher than patients on RT alone (14.9 vs 11.2 months) [30]. This finding was later confirmed in a subgroup analysis, which demonstrated the benefit of RT+TMZ for patients with a methylated *MGMT* promoter compared to those with an unmethylated *MGMT* promoter. [31]. In the same line, Minniti et al. carried out a phase II study of short-course RT (40 Gy in 15 fractions over 3 weeks) plus concomitant and adjuvant TMZ in elderly patients (> 70 years old) with GBM. The median OS was 12.4 months, with a clearly superior benefit in patients with methylated *MGMT* promoter vs patients with

unmethylated *MGMT* promoter (15.8 vs 8.8 months) [32]. These consistent results reinforce that RT plus TMZ is a feasible and effective therapeutic option in elderly patients. Furthermore, *MGMT* promoter status is a useful predictive prognostic marker associated with improved response to this therapeutic combination.

Nevertheless, the management of GBM in newly diagnosed elderly patients is not standardized, leading to considerable debate regarding the best treatment approach. A recent Cochrane Review summarized evidence on the most effective approaches in this population. It found that hypofractionated RT and TMZ alone both provide similar benefit in terms of OS, although it is essential to consider the *MGMT* status [33]. According to this meta-analysis, the combination RT plus TMZ is recommended for patients with a good overall condition and methylated *MGMT* promoter, while short-course RT is recommended in patients with unmethylated *MGMT* promoter. In addition, Mazarakis et al. emphasized that chronological age alone should not drive treatment selection in elderly patients with GBM; instead, decisions should integrate performance status, geriatric fitness, comorbidity burden, patient preferences, and *MGMT* promoter methylation status [25].

A recent pooled analysis including data from the studies NOA-08, Nordic and CE.6 identified additional factors that could improve individualized treatment recommendations. This study included almost 1300 patients diagnosed with GBM and older than 60 years. It confirmed the influence of known clinical prognostic factors -such as EOR and WHO performance status, glucocorticoids (GC) use and *MGMT* promoter methylation status- on patients' prognosis. Furthermore, it identified that comorbidities such as hypertension, diabetes, and/or stroke are associated with worse survival in TMZ-treated patients. The OS of TMZ-treated patients with ≥ 2 comorbidities was comparable to those on RT alone, thus suggesting that the use of TMZ in this group of patients should be reconsidered. In addition, cognitive function at baseline was also identified as a prognostic factor for OS after adjusting. The authors underline the need to systematically perform a CGA and the consideration of comorbidities as an essential part in the decision-making process in the neuro-oncology geriatric field [26].

The available evidence can be summarized in a practical algorithm (Fig. 1). In elderly patients with GBM should be considered the functional status and the *MGMT* promoter methylation status for treatment choice. In patients with > 1 vascular comorbidity (hypertension, diabetes or stroke) treated with TMZ, caution is advised, and it should be considered other therapeutic options with less toxicity associated [34, 35]. CGA, together with *MGMT* status and cognitive evaluation, is established as a decisive tool for therapeutic selection and individualized support for elderly patients with GBM.

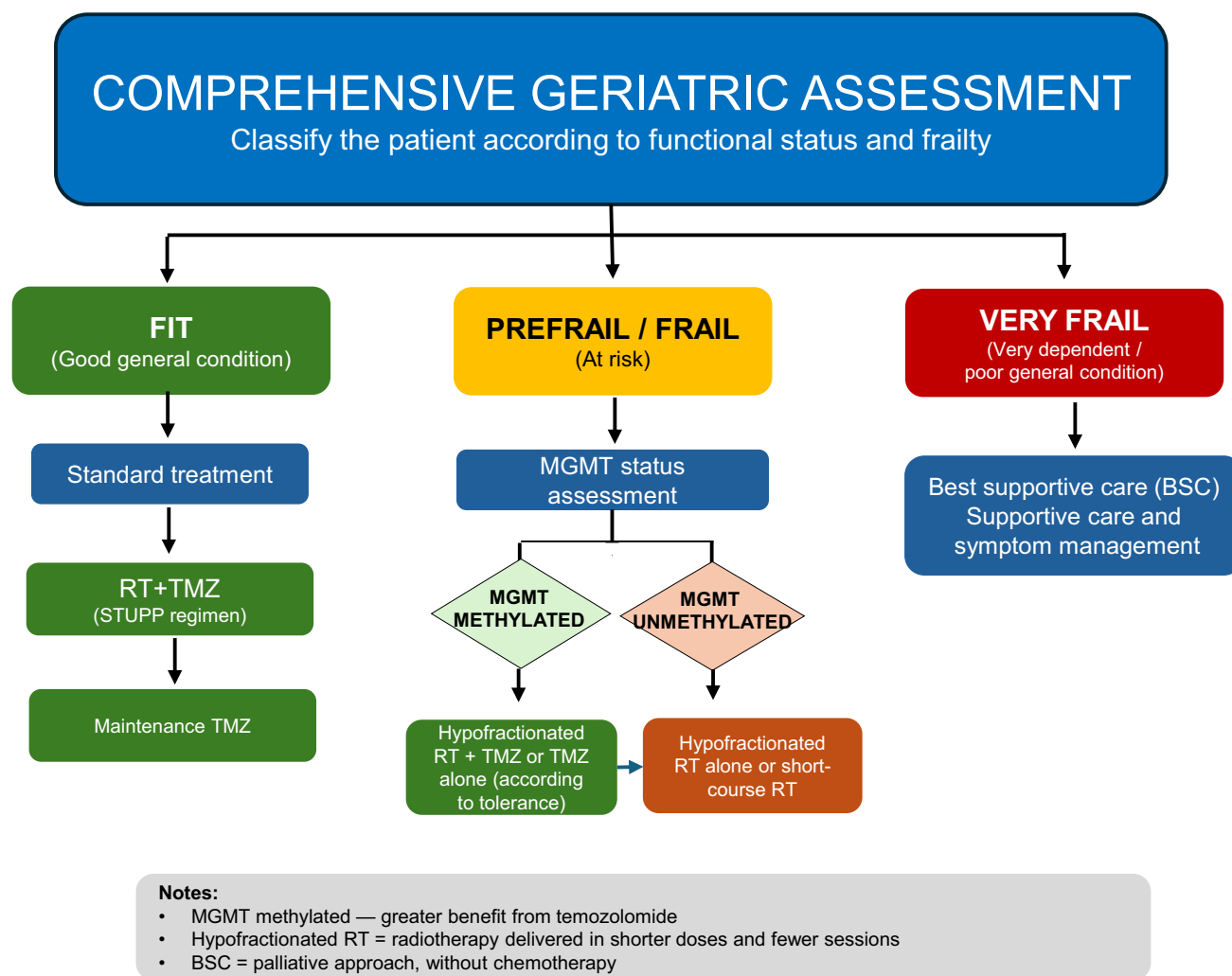


Fig. 1 Algorithm of initial treatment of glioblastoma in elderly patients. In eligible patients, further treatments may be considered

Intermediate-frequency electric field therapy (Tumor Treating Fields or TTFields) has emerged as an effective strategy in combination with TMZ during the maintenance phase, following standard chemoradiotherapy in adult patients with newly diagnosed GBM. The pivotal study EF-14 demonstrated that in patients with GBM who received standard chemoradiotherapy, the addition of TTFields to maintenance TMZ chemotherapy significantly improved both PFS and OS compared to maintenance TMZ alone [36, 37]. A subgroup analysis of the EF-14 study evaluated the safety and efficacy of TTFields in elderly patients (≥ 65 years). It found that combining TTFields with maintenance TMZ significantly improved both PFS (6.5 vs. 3.9 months; HR 0.47; $p = 0.0236$) and OS (17.4 vs. 13.7 months; HR 0.51; $p = 0.0204$) without significant increases in systemic toxicity. The only TTFields-related adverse events were reversible mild/

moderate scalp skin reactions [38]. Regarding treatment adherence, patients with $\geq 75\%$ daily usage had a significantly longer OS: 21.7 months compared to 12.5 months in those with lower compliance. Within this cohort, the subgroup of 59 patients ≥ 70 years of age (39 TTFields+TMZ and 20 TMZ alone) also showed benefit in both OS (14.0 vs. 8.2 months, HR 0.29; $p = 0.0175$), and PFS (6.7 vs. 3.5 months, HR 0.28; $p = 0.0011$) [38].

Real-world data including more than 1,800 patients ≥ 70 years of age treated with TTFields confirmed the feasibility and safety in selected elderly patients with good functional status, without an impact on QoL [39]. However, social and logistical factors may influence adherence, underscoring the importance of clinical and family support in this population.

Results of main studies on GBM in the elderly can be found on Table 1.

Table 1 Results of main studies on glioblastoma in the elderly

Study	Treatment	Population	PFS	OS	OS methylated <i>MGMT</i> promoter	OS unmethylated <i>MGMT</i> promoter	Comments
Keime-Guibert et al. (2007) [5]	RT 60 Gy vs supportive care	> 70 years, KPS > 70	3.7 mo	7.2 mo (RT) vs 4.2 mo (SC)	–	–	RT improves OS vs. supportive care
Roa et al. (2004) [21]	RT 60 Gy vs 40 Gy/15 fractions	> 60 years, KPS > 50	5.1 mo	5.6 mo vs 5.1 mo	–	–	hypoRT equivalent
NOA-08 study (2012) [15]	RT vs TMZ	≥ 65 years	–	RT 9.6 mo vs TMZ 8.6 mo	TMZ 8.4 mo vs RT 4.6 mo	RT 9.6 mo vs TMZ 3.3 mo	<i>MGMT</i> is predictor of benefit with TMZ
Nordic trial (2012) [22]	RT standard vs hypoRT vs TMZ	> 60 years	–	RT 8.2 mo/hypoRT 8.2 mo/TMZ 9.7 mo	9.7 mo	6.8 mo	HypoRT showed non-inferiority; TMZ is effective in patients with methylated <i>MGMT</i> promoter
Brandes, et al. (2003) [30]	RT ± TMZ/PCV	> 65 years, KPS > 60	10.7 mo	14.9 mo (RT+TMZ)	–	–	Benefits with RT+TMZ
Brandes et al. (2009) [31]	Stupp protocol	> 65 years, KPS > 70	9.5 mo	13.7 mo	NR	13.7 mo	43% methylated <i>MGMT</i> promoter
Minniti et al. (2012) [32]	Hypo RT + TMZ	> 70 years, KPS > 60	6 mo	12.4 mo	15.8 mo	8.8 mo	RT + TMZ feasible and effective
Perry et al. (2017) [24]	Hypo RT ± TMZ (CE.6)	≥ 65 years	5.3 mo vs 3.9 mo	9.3 mo vs 7.6 mo	13.5 mo	7.7 mo	Hypo RT + TMZ new standard
Malmström et al. (2024) [26]	Pooled analysis: NOA-08 + Nordic + CE.6	≥ 60 years	–	Variable depending on comorbidities and <i>MGMT</i>	–	–	Confirms the importance of <i>MGMT</i> ; PS, resection, and comorbidities

hypoRT, hypofractionated radiotherapy; KPS, Karnofsky Performance Scale; *MGMT*, O⁶-methylguanine-DNA-methyltransferase; mo, months; NR, not reached; OS, overall survival; PFS, progression free survival; RT, radiotherapy; SC, supportive care; TMZ, temozolomide

Treatment options for progression/recurrence

Currently, there is no standard treatment for recurrent glioblastoma (rGBM). Therapeutic options should always be assessed by a multidisciplinary team, considering clinical trials as an option and considering that second-line therapy has limited benefit. The median OS in patients > 70 years rarely exceeds 6–8 months even with an active approach. Additionally, the proportion of elderly patients receiving systemic treatment is half that of younger patients [40].

Zanello et al. reported that being ≥ 70 years is not an independent predictor of OS (median 19.6 versus 17.0 months, adjusted HR: 1.17, $p = 0.190$); although the functional status of patients at the time of recurrence is the most important factor determining OS (adjusted HR: 1.52, $p < 0.001$) [41]. Elderly patients with poor KPS (≤ 60) at recurrence do not appear to benefit from local therapies, with a median post-progression survival (PFS) of 14 weeks, but they do benefit from systemic treatment, with a median PFS of 21 weeks. A proactive therapeutic approach could be beneficial for certain elderly and/or frail patients with rGBM [42].

Surgery

To date, no prospective studies have analyzed the impact of rescue surgery in rGBM. Several studies have demonstrated that in elderly populations with rGBM and KPS ≥ 70 , reoperation can positively impact on OS compared to other therapies. Furthermore, reoperation did not lead to an increase in postoperative complications compared to initial surgery. For example, Socha et al. reported that patients with rGBM who underwent reoperation had a median OS of 51 weeks, whereas those who received chemotherapy alone had a median OS of only 21 weeks [40, 42].

Evidence supporting resurgery in older patients with rGBM remains limited to retrospective and highly selected cohorts, as no randomized or prospective elderly-specific studies have demonstrated a survival benefit. In a propensity-matched study of 39 patients aged > 65 years, Fariña Núñez et al. reported longer median overall survival in patients undergoing re-resection than in matched patients managed without further surgery (18.0 vs. 10.1 months; HR 0.60, 95% CI 0.36–0.90; $p = 0.043$) [43]. Similarly, a large national database analysis of older patients found an association between reoperation and longer median survival (12 vs. 5 months), with better outcomes after gross-total than subtotal resection and no substantial increase in overall complication rates [44]. In contrast, Socha et al.

reported a median post-progression survival of 51 weeks with local treatment—surgery and/or radiotherapy—versus 21 weeks with chemotherapy; however, this difference was not statistically significant ($p = 0.36$) [42]. Therefore, reoperation may be considered in carefully selected older patients. Chronological age alone should not preclude surgery, although the available results must be interpreted cautiously because of selection bias and the absence of prospective comparative evidence.

Radiotherapy

Re-irradiation may be considered for selected older patients with rGBM particularly when the recurrence is limited in volume and occurs at least 6 months after the initial radiotherapy course. Although the evidence is restricted to retrospective series, re-irradiation can provide local control and symptomatic relief with acceptable toxicity. In a study of 25 patients aged ≥ 65 years, median OS after re-irradiation was 6.9 months, with symptomatic radionecrosis reported in fewer than 10% of patients. A longer interval from initial radiotherapy was independently associated with improved survival, suggesting that chronological age alone should not exclude re-irradiation in appropriately selected patients [45].

TTFIELDS

TTFIELDS have been approved by the FDA for rGBM based on the EF-11 trial, in which they showed similar OS to chemotherapy but no elderly-specific efficacy analysis. Therefore, their benefit in older patients with recurrent disease remains uncertain, and treatment feasibility should be assessed according to functional and cognitive status, caregiver support, scalp condition, and expected adherence [38, 46].

A post hoc analysis of the phase 3 trial EF-14, showed that adding TTFIELDS to maintenance temozolomide improved PFS and overall OS in patients aged ≥ 65 years, with a similar benefit in those aged ≥ 70 years, without increasing systemic toxicity or impairing QoL. However, these findings apply mainly to selected, functionally preserved patients with KPS ≥ 70 who had completed chemoradiotherapy without progression. Evidence remains limited for frail patients or those with poor performance status [38, 47].

Systemic treatment

In elderly patients with rGBM, the clinical benefit of active therapy is limited and drug tolerability plays a crucial role. No systemic regimen has demonstrated an OS benefit in a randomized trial specifically conducted in older patients

with rGBM. Treatment should therefore be individualized [40–42].

Nitrosoureas

Lomustine remains one of the most commonly used systemic treatments for recurrent glioblastoma. In the EORTC 26101 trial, the combination of lomustine and bevacizumab was compared with lomustine alone. Although the addition of bevacizumab improved median progression-free survival (4.2 vs. 1.5 months), it did not translate into an OS benefit (9.1 vs. 8.6 months) [48]. However, this study was not specifically designed for older patients and did not include a geriatric subgroup analysis. Therefore, its results should be applied cautiously to frail older adults, in whom lomustine-related cumulative myelosuppression may substantially limit treatment and requires close monitoring.

Fotemustine has been evaluated for rGBM in the elderly in phase II trials. It is a common treatment option for patients with rGBM refractory to TMZ. Fotemustine demonstrated a PFS rate at 6 months of approximately 30%. In the population aged > 65 years, a median PFS of 6 months and an OS of 7 months was observed. The most relevant grade 3–4 toxicity events were thrombocytopenia (15.3%) and neutropenia (9.2%) [49, 50]. However, according to the Spanish Medicines Agency (AEMPS) public database (CIMA), the marketing authorization for Mustoforan® (fotemustine) was revoked on January 21, 2025. Therefore, fotemustine is no longer authorized or commercially available in Spain.

Treatment with nitrosoureas is usually reserved for patients with diffuse relapses that do not cause mass effect or for those with methylated *MGMT* promoter status. Its use in the elderly should be reserved for patients with good KPS (≥ 70), preserved hematological and hepatic function, and no relevant comorbidities.

Antiangiogenic agents

Bevacizumab is the most widely studied antiangiogenic agent for rGBM. Its efficacy has been evaluated in multiple clinical trials, including combinations with irinotecan or nitrosoureas. The drug demonstrated an objective response rate of around 30% and a positive impact on PFS, although it did not significantly impact on OS. One retrospective study compared the survival between elderly (age > 70) and non-elderly (age ≤ 70) patients receiving bevacizumab for rGBM and found similar outcomes in both groups. The median PFS was 3.8 months for the elderly compared to 4.1 months for the non-elderly, while the median OS at recurrence was 5.5 months for elderly patients and 6.5 months for their younger counterparts. Bevacizumab is primarily recommended for recurrences that cause a mass

effect, where symptom control is a priority, or for patients with an unmethylated *MGMT* promoter [51].

Another antiangiogenic agent evaluated in rGBM is regorafenib. The REGOMA phase II study, assessed the efficacy and safety of regorafenib vs lomustine in the treatment of recurrent rGBM. This study showed a significantly longer OS in patients receiving regorafenib vs those receiving lomustine (7.4 months vs. 5.6 months). Although regorafenib showed efficacy against lomustine, its safety and efficacy should be established in adequately powered phase 3 studies [52]. However, it is not currently approved by the EMA/AEMPS for rGBM and its use in Spain would be off-label [53, 54]. REGOMA was not designed specifically for older patients. These findings support possible use in selected fit older patients but require prospective confirmation.

Temozolomide

Temozolomide rechallenge may provide modest clinical benefit in selected patients with recurrent glioblastoma, particularly when recurrence occurs more than 4–6 months after completion of prior temozolomide and the tumor is *MGMT* promoter-methylated [55]. However, no prospective data specifically support this strategy in patients aged > 65 years. In older adults, should therefore be considered only in carefully selected patients with adequate bone-marrow reserve, a prolonged treatment-free interval, and *MGMT* promoter methylation, with close hematological monitoring [55].

Targeted therapies

In patients with GBM, mutations such as BRAF V600E or NTRK fusions are rare (<2%). No efficacy data are available specifically for older patients. Molecular testing is most relevant when the patient is fit enough to receive matched therapy or enter a clinical trial, considering comorbidities, drug interactions, toxicity, and treatment goals [40].

Palliative care, supportive care and follow-up

Glioblastoma in the elderly requires initiation of supportive treatment from diagnosis, due to its poor prognosis and early functional decline. Patients can exhibit symptoms such as decreased level of consciousness, changes in mental status, seizures, fever, and dysphagia, alongside motor and sensory neurological deficits, that may be present because of tumor progression throughout evolution [56]. Early use of treatments like corticosteroids and anticonvulsants may be necessary. Furthermore, these patients may experience a diminished QoL and reduced decision-making capacity,

due to cognitive impairment, communication difficulties, and behavioral changes in the early stages of the disease. As the disease progresses, these symptoms can burden the end-of-life of patients and their families, whose involvement in care is essential. The main pharmacological treatments for

palliative care and end-of-life care on GBM in the elderly can be found in Table 2.

National and international scientific societies, such as the American Society of Clinical Oncology (ASCO), recommend palliative care in the advanced stages of cancer.

Table 2 Pharmacological treatments for palliative care and end-of-life care in elderly patients with GBM [68, 69]

Symptom/indication	Drug class	Drug	Recommended use/comments
Pain, headache, cerebral edema	Corticosteroids	Dexamethasone	Treatment of choice for tumor-related edema. Use the minimum effective dose. May worsen comorbidities such as diabetes mellitus, hypertension, and cognitive impairment
	Analgesics	Opioids	Oral, parenteral, or transdermal routes may be used. Common adverse effects include sedation, nausea, vomiting, constipation, urinary retention, respiratory depression, confusion, delirium, and dependence. Use with caution in the elderly
	Anti-VEGF therapy	Bevacizumab	Alternative to corticosteroids for reducing cerebral edema, particularly after radiotherapy. No definitive evidence of survival benefit
Epilepsy	Antiepileptic drugs	Levetiracetam	Preferred first-line monotherapy due to lower failure rate and fewer drug–drug interactions. Approximately one-third of patients may require add-on therapy
		Midazolam	Intranasal administration for acute seizure control when oral intake is no longer feasible
		Clonazepam	Buccal administration as prophylactic therapy in end-of-life or home-based care when oral intake is not possible
Delirium/agitation	Antipsychotics	Haloperidol	0.25–1 mg PO, up to every 8 h. Use for the shortest duration and at the lowest effective dose
		Olanzapine	2.5–5 mg PO daily. Risk of metabolic effects and QT prolongation
		Risperidone	0.25–0.5 mg PO daily. Increased risk of stroke, falls, and QT prolongation
		Quetiapine	12.5–25 mg PO daily or every 12 h. Sedation and orthostatic hypotension may occur
	Sedation	Midazolam	May be used for palliative sedation in refractory delirium
Nausea/vomiting	Prokinetics	Metoclopramide	Higher risk of extrapyramidal symptoms and falls in elderly patients
	Serotonin antagonists	Ondansetron	Preferred alternative to metoclopramide due to better safety profile
Mood and behavioral disorders	Antidepressants (SSRIs)	Fluoxetine, Sertraline, Citalopram	May increase risk of ataxia, falls, syncope, QT prolongation, and gastrointestinal bleeding, especially with aspirin, anticoagulants, or NSAIDs
	Antidepressants (SNRIs)	Venlafaxine, Duloxetine	Preferred over SSRIs when feasible; consider concomitant use of proton pump inhibitors (PPIs)
	Other antidepressants	Mirtazapine	Maybe considered in patients receiving anticoagulant therapy

Reported doses are indicative and should be individualized according to patient frailty, comorbidities, and clinical context

VEGF, vascular endothelial growth factor; NSAIDs, nonsteroidal anti-inflammatory drugs; PO, *per os*, orally; SNRIs, serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors

Although several clinical guidelines are available, none are aimed to improve the physical, psychosocial, and spiritual needs of patients with gliomas and their caregivers [57–59]. Advance care planning, including the registration of advance directives, is highly recommended for these patients. This process helps to define objectives and preferences in the final stages of the disease and identify patient representatives. Research has shown that advance care planning can improve QoL and satisfaction among patients and their caregivers [60, 61].

A recent study including 107 patients aged ≥ 80 years with GBM identified the most common symptoms and signs among the elderly. These include motor deficits (53%), psychiatric symptoms and cognitive changes (42%), aphasia (30%), seizures (26%), visual disturbances (15%), headaches (14%), and sensory deficits (14%). Other presenting symptoms included nausea, incontinence, vertigo, falls, hypoacusis, strabismus, dysphagia, and weight loss (16%). Only 2% of patients presented with asymptomatic tumors; however, any of the above symptoms and signs may develop as the disease progresses [62]. Consequently, palliative care for these patients should consider many areas to be comprehensive.

Regarding pharmacological management in elderly patients, two important measures should be considered initially: (1) avoid polypharmacy, and (2) monitor for potential drug-drug interactions. Benzodiazepines should not be the first choice for insomnia due to the increased risk of delirium and falls. Corticosteroids, preferably dexamethasone, in one or two doses, should be administered at the minimum dose required, with gastric protection, and its administration may worsen other comorbidities, such as Diabetes Mellitus, high blood pressure and cognitive function. Metoclopramide carries a higher risk of extrapyramidal effects and falls, it is preferable the use of serotonin antagonists such as ondansetron. Histamine-2 receptor antagonists such as famotidine and ranitidine can cause delirium, worsen dementia and impair cognitive status, being the proton pump inhibitors (PPIs) a preferable alternative if necessary. Selective serotonin reuptake inhibitor (SSRI) antidepressants such as fluoxetine, sertraline, or citalopram may induce ataxia, increase the risk of falls and syncope, extend the QT interval, and increase the risk of gastrointestinal bleeding, especially with concomitant use of aspirin, anticoagulants, or nonsteroidal anti-inflammatory drugs (NSAIDs). It is preferable to use serotonin and norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine or duloxetine, or at least its concomitant use with PPIs. Additionally, mirtazapine should be considered in patients undergoing anticoagulant therapy.

Antipsychotic drugs such as haloperidol, chlorpromazine, olanzapine, quetiapine, or risperidone may have anticholinergic effects, increase the risk of stroke, hyperglycemia, falls, and fractures, and extend the QT interval. It is recommended to use antipsychotic drugs for as short a time as possible and

at the lowest possible dose (e.g., haloperidol 0.25–1 mg PO up to every 8 h, olanzapine 2.5–5 mg PO daily, risperidone 0.25–0.5 mg PO daily, or quetiapine 12.5–25 mg PO daily or every 12 h). The use of opioids may be necessary for pain control, although their side effects, such as sedation, nausea, vomiting, constipation, urinary retention, respiratory depression, dependence, confusion, and delirium, may be more frequent in the elderly population. Other drugs such as paracetamol or NSAIDs are preferred when possible [58, 59].

Antiepileptic drugs play a crucial role in the management of brain tumor-related epilepsy. As in young people, its prophylactic use is not recommended, but treatment with antiepileptic drugs should be initiated after the onset of the first seizure. Levetiracetam as monotherapy is an effective option, with a lower failure rate and fewer drug interactions. It is generally preferred for both focal and bilateral tonic-clonic seizures. However, approximately one-third of patients will require a second line due to persistent seizures despite dose escalation. Other agents such as lacosamide, lamotrigine, and valproic acid provide similar efficacy to levetiracetam and are generally added for seizure control when monotherapy fails. Additionally, new drugs such as brivaracetam and perampanel are effective when used in combination. In the final stage of the disease, when oral administration is no longer feasible, intranasal midazolam, as an emergency treatment, and buccal clonazepam, as prophylactic, can be an option for home-based care [63].

Other treatment options for symptom relief, when feasible, include reirradiation of the brain, surgical tumor resection to relieve pressure, or administration of an antiedema agent such as bevacizumab, although there is no definitive evidence of improved survival [64–66].

Regarding follow-up of patients undergoing active treatment, the RANO 2.0 response assessment criteria recommend continuous neurological monitoring and contrast enhanced MRI every 2–3 months, preferably using the same imaging equipment, like the recommendations for younger patients [67].

Limitations

This article is an expert consensus, consequently, the literature search and study selection were not performed using a predefined, reproducible systematic methodology. Evidence specifically involving older adults remains limited; many studies included, use heterogeneous age cut-offs, select patients with relatively good performance status, and report subgroup or retrospective analyses. Direct comparisons between treatment strategies are consequently constrained, and data on frail patients, cognition, QoL, caregiver burden, and real-world implementation are sparse. Therefore, the conclusions and recommendations partly reflect the

clinical judgement and experience of the authors and should be interpreted as expert guidance rather than as definitive evidence-based recommendations.

Conclusions

In conclusion, optimal care of elderly patients with GBM requires early integration of supportive and palliative care and proactive symptom control. Attention should be paid to pharmacological use and interactions, specially involving corticosteroids, antiepileptic drugs, anticoagulants, and psychotropic medications. Careful medication selection, dose adjustment, and regular treatment review are essential to minimize toxicity, cognitive impairment, and functional decline.

Given the heterogeneity among older patients, future research should continue to refine risk stratification, incorporate geriatric assessment tools, and develop treatment strategies that balance survival benefit with preservation of QoL and functional independence.

Acknowledgements We would like to thank Alba Gómez, PhD, and Carmen Aguilar-Gurrieri, PhD, on behalf of Springer Health+, who provided support in the medical writing.

Author contributions Idoia Morilla: conceptualization, investigation, methodology, project administration, supervision, validation, writing—original draft, writing—review and editing. Edinson Caviedes: conceptualization, investigation, methodology, project administration, supervision, writing—review and editing. Regina Gironés Sarrió: conceptualization, visualization, writing—original draft, writing—review and editing. Borja López de San Vicente Hernández, conceptualization, visualization, writing—original draft, writing—review and editing. Natalia Luque Caro: investigation, visualization, writing—original draft, writing—review and editing. Sonia del Barco: conceptualization, investigation, methodology, project administration, supervision, writing—original draft, writing—review and editing. Juana M. Cano: conceptualization, methodology, validation, writing—original draft, writing—review and editing. M. Ángeles Vaz-Salgado: conceptualization, project administration, supervision, visualization, writing—original draft, writing—review and editing.

Funding The medical writing assistance was funded by the Sociedad Española de Oncología Médica (SEOM). The present manuscript was funded without restrictions by Novocure and Nutrimedhealth.

Declarations

Conflict of interest Idoia Morilla has received fees for consulting and speaking services from Novocure, and Roche. Regina Gironés has received fees for consulting and attending Congresses from Novocure and Merck. Natalia Luque Caro has received fees for consulting and speaking services from Novocure, Servier and Roche. Sonia del Barco has received fees for consulting from Novocure and attending Congresses from Servier. M. Ángeles Vaz-Salgado has received fees for consulting and speaking services from Novocure and Servier. Edinson Caviedes, Borja López de San Vicente Hernández, and Juana M. Cano, and declare that they have no conflicts of interest.

Ethical approval Not Applicable.

Informed consent Not Applicable.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

1. Grochans S, Cybulska AM, Simińska D, Korbecki J, Kojder K, Chlubek D, et al. Epidemiology of glioblastoma multiforme—literature review. *Cancers (Basel)*. 2022;14:2412. <https://doi.org/10.3390/cancers14102412>.
2. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO classification of tumors of the Central Nervous System: a summary. *Neuro Oncol*. 2021;23:1231–51. <https://doi.org/10.1093/neuonc/noab106>.
3. Ostrom QT, Price M, Neff C, Cioffi G, Waite KA, Kruchko C, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2015–2019. *Neuro Oncol*. 2022;24:v1-95. <https://doi.org/10.1093/neuonc/noac202>.
4. Weller M, Wick W, Aldape K, Brada M, Berger M, Pfister SM, et al. Glioma. *Nat Rev Dis Primers*. 2015;1:15017. <https://doi.org/10.1038/nrdp.2015.17>.
5. 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. <https://doi.org/10.1056/NEJMoa065901>.
6. Ellingson BM, Wen PY, Cloughesy TF. Modified criteria for radiographic response assessment in glioblastoma clinical trials. *Neurotherapeutics*. 2017;14:307–20. <https://doi.org/10.1007/s13311-016-0507-6>.
7. Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan W, et al. IDH1 and IDH2 mutations in gliomas. *N Engl J Med*. 2009;360:765–73. <https://doi.org/10.1056/NEJMoa0808710>.
8. Hegi ME, Diserens A-C, Gorlia T, Hamou M-F, de Tribolet N, Weller M, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med*. 2005;352:997–1003. <https://doi.org/10.1056/NEJMoa043331>.
9. Brennan CW, Verhaak RGW, McKenna A, Campos B, Nounmeh H, Salama SR, et al. The somatic genomic landscape of glioblastoma. *Cell*. 2013;155:462–77. <https://doi.org/10.1016/j.cell.2013.09.034>.
10. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJB, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352:987–96. <https://doi.org/10.1056/NEJMoa043330>.

11. Niyazi M, Brada M, Chalmers AJ, Combs SE, Erridge SC, Fioren-
tino A, et al. ESTRO-ACROP guideline “target delineation of
glioblastomas.” *Radiother Oncol.* 2016;118:35–42. <https://doi.org/10.1016/j.radonc.2015.12.003>.
12. Xue Q-L. The frailty syndrome: definition and natural history.
Clin Geriatr Med. 2011;27:1–15. <https://doi.org/10.1016/j.cger.2010.08.009>.
13. Lombardi G, Bergo E, Caccese M, Padovan M, Bellu L, Brunello
A, et al. Validation of the comprehensive geriatric assessment as
a predictor of mortality in elderly glioblastoma patients. *Cancers*
(Basel). 2019;11:1509. <https://doi.org/10.3390/cancers11101509>.
14. Weller M, van den Bent M, Tonn JC, Stupp R, Preusser M, Cohen-
Jonathan-Moyal E, et al. European Association for Neuro-Oncology
(EANO) guideline on the diagnosis and treatment of adult astrocytic
and oligodendroglial gliomas. *Lancet Oncol.* 2017;18:e315–29.
[https://doi.org/10.1016/s1470-2045\(17\)30194-8](https://doi.org/10.1016/s1470-2045(17)30194-8).
15. Wick W, Platten M, Meisner C, Felsberg J, Tabatabai G, Simon
M, et al. Temozolomide chemotherapy alone versus radiother-
apy alone for malignant astrocytoma in the elderly: the NOA-
08 randomised, phase 3 trial. *Lancet Oncol.* 2012;13:707–15.
[https://doi.org/10.1016/S1470-2045\(12\)70164-X](https://doi.org/10.1016/S1470-2045(12)70164-X).
16. Minniti G, Lombardi G, Paolini S. Glioblastoma in elderly
patients: current management and future perspectives. *Cancers*
(Basel). 2019;11:336. <https://doi.org/10.3390/cancers11030336>.
17. Laigle-Donadey F, Metellus P, Guyotat J, Menei P, Proust F,
Dufour H, et al. Surgery for glioblastomas in the elderly: an
Association des Neuro-oncologues d’Expression Française
(ANOCEF) trial. *J Neurosurg.* 2023;138:1199–205. <https://doi.org/10.3171/2022.8.JNS221068>.
18. Heiland DH, Haaker G, Watzlawick R, Delev D, Masalha W,
Franco P, et al. One decade of glioblastoma multiform surgery
in 342 elderly patients: what have we learned? *J Neurooncol.*
2018;140:385–91. <https://doi.org/10.1007/s11060-018-2964-8>.
19. Klingenschmid J, Krigers A, Kerschbaumer J, Thomé C, Ping-
gera D, Freyschlag CF. Surgical management of malignant
glioma in the elderly. *Front Oncol.* 2022;12:900382. <https://doi.org/10.3389/fonc.2022.900382>.
20. Löfgren D, Valachis A, Olivecrona M. Risk for morbidity and
mortality after neurosurgery in older patients with high grade
gliomas - a retrospective population-based study. *BMC Geriatr.*
2022;22:805. <https://doi.org/10.1186/s12877-022-03478-6>.
21. Roa W, Brasher PMA, Bauman G, Anthes M, Bruera E, Chan A,
et al. Abbreviated course of radiation therapy in older patients
with glioblastoma multiforme: a prospective randomized clinical
trial. *J Clin Oncol.* 2004;22:1583–8. <https://doi.org/10.1200/JCO.2004.06.082>.
22. Malmström A, Grønberg BH, Marosi C, Stupp R, Frappaz D,
Schultz H, et al. Temozolomide versus standard 6-week radio-
therapy versus hypofractionated radiotherapy in patients older
than 60 years with glioblastoma: the Nordic randomised, phase
3 trial. *Lancet Oncol.* 2012;13:916–26. [https://doi.org/10.1016/S1470-2045\(12\)70265-6](https://doi.org/10.1016/S1470-2045(12)70265-6).
23. Roa W, Kepka L, Kumar N, Sinaika V, Matiello J, Lomidze
D, et al. International atomic energy agency randomized phase
III study of radiation therapy in elderly and/or frail patients
with newly diagnosed glioblastoma multiforme. *J Clin Oncol.*
2015;33:4145–50. <https://doi.org/10.1200/JCO.2015.62.6606>.
24. Perry JR, Laperriere N, O’Callaghan CJ, Brandes AA, Menten
J, Phillips C, et al. Short-course radiation plus temozolo-
mide in elderly patients with glioblastoma. *N Engl J Med.*
2017;376:1027–37. <https://doi.org/10.1056/nejmoa1611977>.
25. Mazarakis NK, Robinson SD, Sinha P, Koutsarnakis C,
Komaitis S, Stranjalis G, et al. Management of glioblastoma in
elderly patients: a review of the literature. *Clin Transl Radiat*
Oncol. 2024;46:100761. <https://doi.org/10.1016/j.ctro.2024.100761>.
26. Malmström A, Oppong FB, Ocallaghan CJ, Wick W, Laperriere
N, Gorlia T, et al. Prognostic factors for overall survival in elderly
patients with glioblastoma: analysis of the pooled NOA-08 and
Nordic trials with the CCTG-EORTC (CE6) trial. *Neurooncol*
Adv. 2024;6:vdae211. <https://doi.org/10.1093/noajnl/vdae211>.
27. Lüttendorf-Caucig C, Freyschlag C, Masel EK, Marosi C. Guid-
ing treatment choices for elderly patients with glioblastoma by a
comprehensive geriatric assessment. *Curr Oncol Rep.* 2020;22:93.
<https://doi.org/10.1007/s11912-020-00951-6>.
28. Krenzlin H, Jankovic D, Alberter C, Kalasauskas D, Westphalen
C, Ringel F, et al. Frailty in glioblastoma is independent from
chronological age. *Front Neurol.* 2021;12:777120. <https://doi.org/10.3389/fneur.2021.777120>.
29. Chahal M, Thiessen B, Mariano C. Treatment of older adult
patients with glioblastoma: moving towards the inclusion of a
comprehensive geriatric assessment for guiding management.
Curr Oncol. 2022;29:360–76. <https://doi.org/10.3390/curroncol29010032>.
30. Brandes AA, Vastola F, Basso U, Berti F, Pinna G, Rotilio A,
et al. A prospective study on glioblastoma in the elderly. *Cancer.*
2003;97:657–62. <https://doi.org/10.1002/cncr.11097>.
31. Brandes AA, Franceschi E, Tosoni A, Benevento F, Scopece
L, Mazzocchi V, et al. Temozolomide concomitant and adju-
vant to radiotherapy in elderly patients with glioblastoma: cor-
relation with MGMT promoter methylation status. *Cancer.*
2009;115:3512–8. <https://doi.org/10.1002/cncr.24406>.
32. Minniti G, Lanzetta G, Scaringi C, Caporello P, Salvati M, Arcella
A, et al. Phase II study of short-course radiotherapy plus concomi-
tant and adjuvant temozolomide in elderly patients with glioblas-
toma. *Int J Radiat Oncol Biol Phys.* 2012;83:93–9. <https://doi.org/10.1016/j.ijrobp.2011.06.1992>.
33. Hanna C, Lawrie TA, Rogozińska E, Kernohan A, Jefferies S,
Bulbeck H, et al. Treatment of newly diagnosed glioblastoma in
the elderly: a network meta-analysis. *Cochrane Database Syst Rev.*
2020;3:CD013261. <https://doi.org/10.1002/14651858.CD013261.pub2>.
34. Liu Y, Ma L, Fu X, Zhang Y, Zheng J, Chen Z. Safety assess-
ment of temozolomide: real-world adverse event analysis from
the FAERS database. *Front Pharmacol.* 2025;16:1578406. <https://doi.org/10.3389/fphar.2025.1578406>.
35. Zhou Y, Jia P, Fang Y, Zhu W, Gong Y, Fan T, et al. Comprehen-
sive understanding of the adverse effects associated with temozo-
lomide: a disproportionate analysis based on the FAERS database.
Front Pharmacol. 2024;15:1437436. <https://doi.org/10.3389/fphar.2024.1437436>.
36. Stupp R, Taillibert S, Kanner AA, Kesari S, Steinberg DM, Toms
SA, et al. Maintenance therapy with tumor-treating fields plus
temozolomide vs temozolomide alone for glioblastoma. *JAMA.*
2015;314:2535. <https://doi.org/10.1001/jama.2015.16669>.
37. Stupp R, Taillibert S, Kanner A, Read W, Steinberg DM, Lher-
mitte B, et al. Effect of tumor-treating fields plus maintenance
temozolomide vs maintenance temozolomide alone on survival
in patients with glioblastoma. *JAMA.* 2017;318:2306. <https://doi.org/10.1001/jama.2017.18718>.
38. Ram Z, Kim C-Y, Hottinger AF, Idhah A, Nicholas G, Zhu J-J.
Efficacy and safety of tumor treating fields (TTFields) in elderly
patients with newly diagnosed glioblastoma: subgroup analysis
of the phase 3 EF-14 clinical trial. *Front Oncol.* 2021;11:671972.
<https://doi.org/10.3389/fonc.2021.671972>.
39. Regev O, Merkin V, Blumenthal DT, Melamed I, Kaisman-Elbaz
T. Tumor-treating fields for the treatment of glioblastoma: a sys-
tematic review and meta-analysis. *Neurooncol Pract.* 2021;8:426–
40. <https://doi.org/10.1093/nop/npab026>.
40. Prajapati HP, Singh DK. Recurrent glioblastoma in elderly:
options and decision for the treatment. *Surg Neurol Int.*
2022;13:397. https://doi.org/10.25259/SNI_552_2022.

41. Zanello M, Roux A, Ursu R, Peeters S, Bauchet L, Noel G, et al. Recurrent glioblastomas in the elderly after maximal first-line treatment: does preserved overall condition warrant a maximal second-line treatment? *J Neurooncol.* 2017;135:285–97. <https://doi.org/10.1007/s11060-017-2573-y>.
42. Socha J, Kepka L, Ghosh S, Roa W, Kumar N, Sinaika V, et al. Outcome of treatment of recurrent glioblastoma multiforme in elderly and/or frail patients. *J Neurooncol.* 2016;126:493–8. <https://doi.org/10.1007/s11060-015-1987-7>.
43. Fariña Nuñez MT, Franco P, Cipriani D, Neidert N, Behringer SP, Mader I, et al. Resection of recurrent glioblastoma multiforme in elderly patients: a pseudo-randomized analysis revealed clinical benefit. *J Neurooncol.* 2020;146:381–7. <https://doi.org/10.1007/s11060-020-03393-z>.
44. Chen Y-R, Sole J, Ugiliweneza B, Johnson E, Burton E, Woo SY, et al. National trends for reoperation in older patients with glioblastoma. *World Neurosurg.* 2018;113:e179–89. <https://doi.org/10.1016/j.wneu.2018.01.211>.
45. Straube C, Antoni S, Gempt J, Zimmer C, Meyer B, Schlegel J, et al. Re-irradiation in elderly patients with glioblastoma: a single institution experience. *J Neurooncol.* 2019;142:327–35. <https://doi.org/10.1007/s11060-019-03101-6>.
46. Stupp R, Wong ET, Kanner AA, Steinberg D, Engelhard H, Heidecke V, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. *Eur J Cancer.* 2012;48:2192–202. <https://doi.org/10.1016/j.ejca.2012.04.011>.
47. Ram Z, Kim C-Y, Hottinger AF, Idubai A, Nicholas G, Zhu J-J. Corrigendum: efficacy and safety of tumor treating fields (TTFs) in elderly patients with newly diagnosed glioblastoma: subgroup analysis of the phase 3 EF-14 clinical trial. *Front Oncol.* 2022. <https://doi.org/10.3389/fonc.2022.902929>.
48. Wick W, Gorlia T, Bendszus M, Taphoorn M, Sahm F, Harting I, et al. Lomustine and bevacizumab in progressive glioblastoma. *N Engl J Med.* 2017;377:1954–63. <https://doi.org/10.1056/nejmoa1707358>.
49. Addeo R, Lamberti G, Simonetti G, Iodice P, Marinelli A, Montella L, et al. Biweekly fotemustine schedule for recurrent glioblastoma in the elderly: activity and toxicity assessment of a multicenter study. *CNS Oncol.* 2019;8:CNS32–CNS32. <https://doi.org/10.2217/cns-2019-0004>.
50. Santoni M, Scoccianti S, Lolli I, Fabrini MG, Silvano G, Detti B, et al. Efficacy and safety of second-line fotemustine in elderly patients with recurrent glioblastoma. *J Neurooncol.* 2013;113:397–401. <https://doi.org/10.1007/s11060-013-1125-3>.
51. Barrascout E, Lamuraglia M. Glioblastoma and bevacizumab in elderly patients: monocentric study. *J Oncol Pharm Pract.* 2021;27:842–6. <https://doi.org/10.1177/1078155220940396>.
52. Lombardi G, De Salvo GL, Brandes AA, Eoli M, Rudà R, Faedi M, et al. Regorafenib compared with lomustine in patients with relapsed glioblastoma (REGOMA): a multicentre, open-label, randomised, controlled, phase 2 trial. *Lancet Oncol.* 2019;20:110–9. [https://doi.org/10.1016/S1470-2045\(18\)30675-2](https://doi.org/10.1016/S1470-2045(18)30675-2).
53. European Medicines Agency. Stivarga n.d.
54. Agencia Española de Medicamentos y Productos Sanitarios. Stivarga. Ficha técnica n.d.
55. Weller M, Tabatabai G, Kästner B, Felsberg J, Steinbach JP, Wick A, et al. MGMT promoter methylation is a strong prognostic biomarker for benefit from dose-intensified temozolomide rechallenge in progressive glioblastoma: the DIRECTOR trial. *Clin Cancer Res.* 2015;21:2057–64. <https://doi.org/10.1158/1078-0432.CCR-14-2737>.
56. Al-Ghaithi AM, Al-Barkhati S, Al Abri AM, Al Husaini D, Al-Hajri A, Al-Saadi T. Palliative care in patients with glioblastoma: a systematic review. *Med Int.* 2025;5:46. <https://doi.org/10.3892/mi.2025.245>.
57. Sanders JJ, Temin S, Ghoshal A, Alesi ER, Ali ZV, Chauhan C, et al. Palliative care for patients with cancer: ASCO guideline update. *J Clin Oncol.* 2024;42:2336–57. <https://doi.org/10.1200/JCO.24.00542>.
58. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Palliative care V.3.2026. © National Comprehensive Cancer Network, Inc. 2026. All rights reserved. Accessed August 2026. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
59. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Older Adult Oncology V.1.2026. © National Comprehensive Cancer Network, Inc. 2026. All rights reserved. Accessed August 2026. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
60. Okon II, Osama M, Akpan A, Fabrini Paleare LF, Ferreira MY, Shafqat MD, et al. The evolving role of palliative care in older people with glioblastoma. *World Neurosurg.* 2024;192:140–9. <https://doi.org/10.1016/j.wneu.2024.09.125>.
61. Brinkman-Stoppelenburg A, Rietjens JAC, van der Heide A. The effects of advance care planning on end-of-life care: a systematic review. *Palliat Med.* 2014;28:1000–25. <https://doi.org/10.1177/0269216314526272>.
62. Stadler C, Gramatzki D, Le Rhun E, Hottinger AF, Hundsberger T, Roelcke U, et al. Glioblastoma in the oldest old: clinical characteristics, therapy, and outcome in patients aged 80 years and older. *Neuro-oncol Pract.* 2024;11:132–41. <https://doi.org/10.1093/nop/npad070>.
63. van der Meer PB, Taphoorn MJB, Koekkoek JAF. Management of epilepsy in brain tumor patients. *Curr Opin Oncol.* 2022;34:685–90. <https://doi.org/10.1097/CCO.0000000000000876>.
64. Kazda T, Hnidakova L, Minniti G. Reirradiation in recurrent glioblastoma. *Curr Opin Oncol.* 2025;37:580–8. <https://doi.org/10.1097/CCO.0000000000001192>.
65. Voisin MR, Zuccato JA, Wang JZ, Zadeh G. Surgery for recurrent glioblastoma multiforme: a retrospective case control study. *World Neurosurg.* 2022;166:e624–31. <https://doi.org/10.1016/j.wneu.2022.07.070>.
66. Fu M, Zhou Z, Huang X, Chen Z, Zhang L, Zhang J, et al. Use of bevacizumab in recurrent glioblastoma: a scoping review and evidence map. *BMC Cancer.* 2023;23:544. <https://doi.org/10.1186/s12885-023-11043-6>.
67. Pineda Ibarra C, Oleaga Zufiria L, Valduvicio Ruiz I, Pineda Losada E, Pujol Farré T, González Ortiz S. RANO 2.0: update to the response assessment for gliomas. *Radiología (English Edition).* 2025;67:101621. <https://doi.org/10.1016/j.rxeng.2025.101621>.
68. Pace A, Dirven L, Koekkoek JAF, Golla H, Fleming J, Rudà R, et al. European Association for Neuro-Oncology (EANO) guidelines for palliative care in adults with glioma. *Lancet Oncol.* 2017;18:e330–40. [https://doi.org/10.1016/S1470-2045\(17\)30345-5](https://doi.org/10.1016/S1470-2045(17)30345-5).
69. Koekkoek JAF, van der Meer PB, Pace A, Hertler C, Harrison R, Leeper HE, et al. Palliative care and end-of-life care in adults with malignant brain tumors. *Neuro Oncol.* 2023;25:447–56. <https://doi.org/10.1093/neuonc/noac216>.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.