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Current clinical management of elderly patients with glioma

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Abstract

Introduction: The incidence of gliomas is increasing in elderly patients. Clinical factors, such as age, performance status, and comorbidities contribute when choosing adequate treatment in older patients.

Areas covered: This review covers the main pathological and molecular features of gliomas in elderly patients, as well as the neurological and geriatric assessment to select patients for surgery and antineoplastic treatments. The results from the most relevant clinical trials in both lower-grade (LGGs) and high-grade gliomas (HGGs) are reviewed.

Expert opinion: Different clinical and biological factors need to be integrated into prognostic scales in order to better stratify the elderly population. Both Stupp and Perry regimens can be proposed to fit patients with GBM aged < 70 years. Conversely, for patients aged ≥ 70 years, the Perry regimen should be preferred. For unfit and frail patients, temozolomide alone when MGMT is methylated or hypofractionated RT alone when MGMT is unmethylated, are the optimal choice. Few data are available regarding the optimal management of elderly patients with LGGs. The benefit of an extensive resection and presence of methylation of the MGMT promoter need to be further investigated to confirm their role in improving the OS.

Keywords: antineoplastic treatments; clinical trials; elderly patients; high-grade gliomas; lower-grade gliomas; selection criteria; surgery

Article highlights:

- Age is not sufficient to define a patient as “elderly”. Clinical, radiological, and molecular factors must be integrated in standardized scales to better stratify patients that may benefit from antineoplastic treatments. Moreover, these prognostic scales need to be validated in prospective cohorts
- The c-IMPACT 3 and 5 updates have suggested the integration of different molecular markers to stratify IDH wild-type and IDH mutant gliomas with different outcomes in terms of survival. These advances will be included in the 2021 WHO Classification leading to a more personalized diagnosis, and therefore a personalized therapy
- The extent of resection (EOR) is a strong predictor of survival in elderly population with GBM. A maximal resection, that includes contrast-enhanced and non-contrast-enhanced lesion can further improve the overall survival in specific subpopulations of elderly patients. Further investigation must be performed to validate the prognostic value of the EOR in elderly lower-grade gliomas.
- The Perry regimen represents the standard of care for patients aged ≥ 70 years, particularly in MGMT methylated patients, while the Stupp regimen may be considered for fit patients aged between 65 to 69 years. For unfit and frail patients, TMZ alone when MGMT is methylated or hypofractionated RT alone when MGMT is unmethylated, are the optimal choices.

1. Introduction

The worldwide aging of the population has led to an increasing incidence of gliomas in patients ≥ 65 years [1]. The relationship between aging and cancer have been largely investigated in terms of immune senescence, telomere shortening, chronic inflammation with antigen stimulation, and genomic instability [2,3]. The aging process differs across the population due to differences in genetics and lifestyle: thus, chronological age does not recapitulate the heterogeneity of the elderly population.

Elderly patients can be classified in 2 different groups: the "early-elderly" (from 66 to 75 years) and the "late elderly" (older than 75 years). In clinical practice, early-elderly patients with good performance status are treated as middle-age patients, but this attitude is based only on clinicians' experience, and standardized recommendations are not available [4]. An old age is not the only factor to consider in glioma patients; however, deficit in activity of daily living, reduced mobility, and cognitive impairment may affect the functional status of patients at the time of diagnosis. Furthermore, elderly patients often have comorbidities, which require polypharmacy with risk of drug interactions and adverse events, that may impair the feasibility of surgery and tolerability of antineoplastic treatments. Last, additional problems, such as impaired vision and/or hearing, lack of adequate social support and lack of education, may further negatively influence the compliance to antineoplastic therapy of elderly patients with gliomas [5].

Overall, the combination of an aggressive tumor biology and large burden of medical and social conditions contribute to a poorer life expectancy in elderly glioma patients. Thus, neuro-oncologists have been forced to personalize treatment options in elderly patients, more often to avoid an undertreatment. Since high-grade gliomas (HGGs) tend to peak in the 60-70 age group and the age is an unfavourable prognostic factor also in lower-grade gliomas (LGGs), a comprehensive geriatric assessment for selecting "fit" patients, who may receive active therapeutic strategies, is needed. In this regard, elderly patients with gliomas were

excluded from most of clinical trials in the past [6], and limited data come from datasets focused on other tumor types.

This review will cover the main pathological and molecular features of HGGs in elderly patients as well as the neurological and geriatric assessment to select patients for surgery and antineoplastic treatments. The results from the most relevant clinical trials will be reviewed. Last, some issues regarding "elderly" LGGs will be discussed.

2. Molecular markers in gliomas of the elderly

The 2016 WHO Classification of Tumors of Central Nervous System has integrated histological and molecular factors in order to stratify patients with different prognosis [7]. Isocitrate dehydrogenase (IDH) 1 and 2 mutations, loss of heterozygosity (LOH) of 1p/19q, inactivation of alpha-thalassemia/mental retardation gene (ATRX), telomerase reverse transcriptase (TERT) mutation, and methylation of the O-6-methylguanine-DNA methyltransferase (MGMT) gene are the main biomarkers employed for diagnostic and prognostic purposes. Mutations of IDH 1 and 2 genes occur early in gliomagenesis, and confer a significantly improved survival [8]. IDH1/2 mutations identify a distinct subset of glioblastomas (GBMs) with an hypermethylation phenotype (G-CIMP) with favorable outcome [9,10], while the absence of IDH mutations in LGGs characterizes an IDH-wild-type subgroup with poorer prognosis [11,12]. Ceccarelli et al reported that IDH mutations are more frequent in younger patients (median age 36-40 years) and almost absent in patients older than 75 years [13]. Considering that the most frequent IDH1 R132H mutation is detectable by immunohistochemistry in about 90% of positive cases, and 5% is represented by IDH2 codon 172 mutation revealed by sequencing, the 2016 WHO Classification has proposed to avoid sequencing for IDH in GBM patients ≥55 years due to the extremely rare frequency of IDH1/2 mutations in older patients. A cost-effectiveness analysis to estimate the financial impact of these guidelines showed that non-R132H mutations were 5.4% only in glioma patients and 0.9% in GBM patients ≥55 years. Therefore, the use of an age-based cutoff for sequencing may lead to significant cost and time savings in daily clinical practice [14].

The 1p/19q codeletion is a marker of grade II and III oligodendrogliomas with a survival ranging approximately from 7 to 15 years, while ATRX loss and absence of 1p/19q codeletion define grade II and III

diffuse astrocytomas [11,15]. Pekmdezci et al reported that ATRX alterations are associated with prolonged survival in typical GBM (IDH wild-type) [16]. However, GBMs with ATRX loss represent a small percentage of all GBM (4.0%): thus, the determination of ATRX loss is not recommended for the elderly population in daily practice.

Hotspot mutations in the TERT promoter lead to an increase of telomerase activity to maintain the immortality of glioma cells. TERT mutations are more frequent in primary GBMs and IDH mutant 1p/19 codeleted oligodendrogliomas (70–83% and 74–78%, respectively) compared with diffuse astrocytomas (10–25%) [17]. The prognostic value of TERT mutations seems to depend on IDH mutational status. TERT mutations designate an unfavorable prognosis within IDHwt GBMs, especially when coupled with homozygous of the rs2853669 C-allele [18,19]. However, Spiegl-Kreinecker et al have demonstrated a prognostic value of TERT mutation in GBM <65 years, but not in those ≥ 65 years. [20]. Moreover, cIMPACT-NOW recommends that LGGs IDH wild-type, whatever grade II or III, that have TERT mutations, should be reclassified as IDH-wild-type diffuse astrocytic gliomas with molecular features of GBM [21]. TP53 mutations have been reported to be age-dependent by Batchelor et al [22], but this study has been performed before the molecular classification of 2016, and the correlation with survival needs to be re-examined.

There are few data on the prognostic importance of other molecular factors, such as CDKN2A homozygous deletion [23], EGFR amplification and chromosome 7 gain plus chromosome 10 loss (+7/-10) [21] in the elderly population.

MGMT gene promotor methylation causes epigenetic silencing of MGMT, an enzyme that is necessary for DNA repair following alkylating agents. MGMT methylation is considered a predictive factor following temozolomide (TMZ): in fact, patients with MGMT methylation show a longer progression-free survival (PFS) and overall survival (OS) compared with unmethylated patients [24]. The predictive value of MGMT methylation has been confirmed in the phase 3 NORDIC and NOA-08 trials [25,26]. More recently, Perry et al have reported a significant advantage of a short course radiotherapy plus temozolomide (TMZ) in elderly patients with MGMT methylated promoter [27].

Recently, Kessler et al have investigated how the molecular profiling in IDH wild-type GBM influence the therapeutic decision in elderly population. Of 253 patients, therapy decision was based on the molecular assessment in 97 (38%) patients. Of these, genetic alteration mostly used for treatment decision were MGMT (n = 68), EGFR (n = 7), CDKN2A/B (n = 8), alterations of the PI3K-AKT-mTOR pathway (n = 5), and BRAF (n = 3) [28].

The methylation of alkylpurine DNA N-glycosylase (APNG) [29] and peroxiredoxin 1 (PRDX1) [30] have been suggested as novel markers for sensitivity to TMZ. In this regard, a post-hoc analysis of the NOA-08 has demonstrated that promoter methylation of both APNG and PRDX1 is virtually absent in elderly malignant astrocytomas, which may partially account for the poorer prognosis of these patients [31].

The Cancer Genome Atlas Network has described 4 distinct subgroups of GBM according to aberrations in gene expression of EGFR, NF1, and PDGFRA/IDH1. The proneural subgroup has a median age of 48.5 years (IC95% 37-57) with 23 patients aged ≤ 40 years and a median OS of 16.2 months, while the classical subgroup had a median age of 57 years with 3 patients only ≤ 40 years and a median OS of 12.2 months (IC95% 10.5-15.0). The mesenchymal and neural subgroups affect patients with a median age of 53 and 55 years, respectively, with similar number of patients aged ≤ 40 years (8 and 5, respectively) and median OS of 15.0 months [32]. Therefore, the proneural signature confers a significantly better prognosis as compared with the other subtypes, and has been suggested to be more prone to respond to bevacizumab in AVAGlio trial [33]. However, elderly patients rarely exhibit a proneural gene expression signature [34]. Conversely, the mesenchymal subtype seems to be less responsive to alkylating agents [35].

Mutations in the H3F3A gene are common in pediatric HGGs: 30% of pediatric GBMs and 60% of diffuse intrinsic pontine gliomas (DIPG) have mutations in this gene; however, no H3F3A mutations were identified in tumor samples from elderly patients in the NOA-08 trial [26].

PD-L1 is highly expressed in GBM [36, 37], but the predictive role of PD-L1 expression on the efficacy of immune checkpoint inhibitors, such as nivolumab or pembrolizumab, remains unclear. Moreover, the prognostic value of PD-L1 expression in GBM is debated [38-40]. The phase III clinical trial Checkmate 143 has shown that nivolumab monotherapy does not improve OS compared with bevacizumab in recurrent GBM previously treated with chemotherapy and radiotherapy. The median PFS was 1.5 months for

nivolumab, and 3.5 months for bevacizumab, while the median OS was 9.8 months for nivolumab, and 10.0 months for bevacizumab. The objective response rate (ORR) was 8% months for nivolumab vs 23% months for bevacizumab [41]. A possible reason of the failure of nivolumab may be the anergic nature of effector T cells to tumor-specific antigens of the tumor microenvironment. In fact, Wherry et al. have investigated the different profile of tumor infiltrating lymphocytes (TILs) in glioma specimens and found that the tumor microenvironment was enriched of CD95, PD-1, PD-L1, CTLA-4, LAG3, and TIM-3, resulting in an immune exhaustion of T cells [42]. Similarly, Reardon et al. displayed that TILs express immunoinhibitory molecules, including CTLA-4 and PD-1, or co-express PD-1 and TIM-3, leading T cells to be less active in recognizing GBM-specific antigens [43]. All these factors contribute to consider GBM as a "cold tumor", and the complicated immunosuppressive networks of the microenvironment make unable the PD-1 checkpoint blockade monotherapy to overcome the factors leading to T cell anergy.

The dysregulation of phosphoinositide 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway occurs in 15-25% of GBM, including mutation or amplification of PI3KCA, PIK3R1, or loss of the tumor suppressor phosphatase and tensin homolog (PTEN) [44]. Inhibition of PI3K pathway has been shown in preclinical models to sensitize glioma cells to the effects of TMZ and radiation [45]. Different clinical trials have evaluated the activity of PI3K/mTOR inhibitors in combination with TMZ and RT, such as voxtalisib [46] and buparlisib [47], reporting a limited evidence of antitumor activity in patients with GBM. The data suggested that blockade of the PI3K/mTOR pathway alone may not be sufficient to impact tumor growth in GBM. Overall, data on efficacy of PI3K/mTOR inhibitors in elderly patients are still missing.

The aim of the 5th edition of the WHO Classification of CNS Tumors, that will appear in 2021, is to provide an integration of molecular data to better stratify gliomas based mainly on the c-IMPACT NOW 3 and 5 updates. The c-IMPACT-NOW 3 promotes the integration of EGFR amplification, TERT promoter mutation, and chromosome 7 gain plus chromosome 10 loss (+7/-10) for identifying among IDH wild-type diffuse astrocytic gliomas those are characterized by an aggressive clinical course similar to GBM, despite appearing histologically as of grade II or III [21]. Similarly, the c-IMPACT-NOW 5 encourages the integration of CDKN2A/B, homozygous deletion, CDK4 amplification, PI3KCA and PIK3R1 mutations, PDGFRA amplification, MYCN amplification, global DNA methylation, and RB1 mutation or deletion to better stratify IDH mutant

gliomas [48]. This new classification based on molecular markers will change the management of gliomas, which will evolve toward a more personalized diagnosis, and therefore personalized therapy.

3. Clinical prognostic factors

Scott et al developed a prognostic flowchart in 437 patients ≥70 years of age with malignant gliomas. The use of different prognostic factors, such as age (< 75.5 years or ≥ 75.5 years), Karnofsky performance status (KPS < 70 or 70-100), and extent of resection (EOR: gross-total/subtotal resection versus biopsy) led to the identification of 4 different prognostic subgroups: subgroup I (patients <75.5 years of age who underwent surgical resection) with survival of 9.3 months; subgroup II (patients ≥75.5 years of age who underwent surgical resection) with survival of 6.4 months; subgroup III (patients with KPS of 70-100 who underwent biopsy) with survival of 4.6 months; subgroup IV (patients with KPS <70 who underwent biopsy) with survival of 2.3 months [49]. A significant limitation of this prognostic scale consists in using clinical factors only and not molecular factors. Moreover, age, KPS, and EOR are not exhaustive to cover the large heterogeneity of elderly population. The Memorial Sloan-Kettering Cancer Center series from 2007 to 2017 revealed in 394 GBM patients of ≥ 65 years that older age, KPS, and EOR were independent prognostic factors, but age alone did not disqualify patients from multimodal therapy including surgical resection, radiotherapy, and chemotherapy [50]. Similarly, among 1067 LGGs aged ≥ 65 years (891 grade II and III astrocytomas, and 176 grade II and III oligodendrogliomas according to WHO 2007) histologic diagnosis and tumor grade displayed a significant prognostic value, while age was found to influence the probability of undergoing surgery, RT, and chemotherapy [51]. Chaicana et al retrospectively reviewed 129 GBM patients aged ≥ 65 years, who underwent GTR or STR from 2007 to 2017, and showed that some preoperative factors, such as KPS < 80, chronic obstructive pulmonary disease, motor deficit, language deficit, cognitive impairment, and tumor size larger than 4 cm were significantly correlated with decreased survival. The combination of these different preoperative factors led to 3 prognostic groups with different outcome: group 1 with a median survival of 9.2 months, group 2 with 5.5 months, and group 3 with 4.4 months, respectively. Based on these results, the Authors suggested that older patients with an increasing number of these factors may not benefit from aggressive surgery as much as patients with fewer factors [52]. A real-

life series of 339 GBM patients aged > 70 years from 2005 to 2015 showed that clinical presentation (Eastern Cooperative Oncology Group performance – ECOG – status ≥ 1, and seizures) and radiological patterns (multifocal tumors and evidence of mass effect) may predict a shorter OS in older GBM patients [53]. Flanigan et al compared clinical and radiological characteristics in non-elderly (< 65 years, 282 patients) and elderly patients (≥ 65 years, 161 patients) with GBM and found that Charlson comorbidities index (CCI), specific comorbidities (insulin dependent diabetes, chronic pulmonary disease, peripheral vascular and cerebrovascular disease), multifocal tumors, and ataxia were predominant in elderly population [54]. Moreover, the Authors identified 5 factors (age > 75 years, weakness, CCI, tumor size, EOR) that predicted OS in multivariate analysis, suggesting that the application of this algorithm could optimize the management of elderly GBM and avoid unnecessary resections in those patients unlikely to receive benefit [54].

Straube et al have integrated some molecular factors (IDH mutations and MGMT methylation status) with clinical and radiological features (age, KPS, seizures, motor deficit and aphasia before and after surgery) in a prognostic score used in 181 newly-diagnosed GBM aged ≥ 65 years. They found that KPS (p 0.005) and MGMT promoter methylation (p 0.013) were the only two factors correlated with better OS [55]. Seizures at presentation are predictors of better survival in both LGGs and young adult HGGs [56,57]. Since the epileptogenic mechanisms seem to be strictly correlated with IDH 1/2 mutations, which are predominant in younger age, preoperative seizures could not play the same role in influencing OS in elderly population.

4. How to best assess an elderly patient?

Considering the poor prognosis of elderly glioma patients, it is of utmost importance the selection of patients fit for surgery and/or antineoplastic therapies in order to achieve an adequate balance between survival benefit and adverse events from treatment. In this regard, no validated tools are available, and the development of standardized scales tailored to elderly population could help neuro-oncologists to distinguish fit from unfit patients. In addition to a detailed neurological examination, the elderly patients need a comprehensive geriatric assessment, which includes domains, such as fatigue, mobility, nutritional status, comorbidities, and social situation to predict tolerability of treatment and survival. All geriatric scales

used in cancer patients can be employed; however, no specific assessment in elderly neurooncological patients has been performed thus far. The American Society of Clinical Oncology (ASCO) drafted in 2015 guidelines for geriatric oncology to predict adverse outcome, suggesting that every patient should undergo an assessment of physiological function, comorbidities, falls, depression, cognition, and nutrition. Clinicians may use different instruments to detect these patients' characteristics, such as instrumental activities of daily living (IADLs), medical history or tools to assess comorbidity, Geriatric Depression Scale (GDS) for depression, the Mini-Cog or the Blessed Orientation-Memory-Concentration test (BOMC) for cognition, and assessment of unintentional weight loss to evaluate nutrition, while short tools, such as Geriatric-8 or Vulnerable Elders Survey-13 (VES-13), can help clinicians to predict mortality [58]. Furthermore, Owusu et al analyzed the efficacy of ECOG Performance Status and KPS scales to identify abnormalities on Comprehensive Geriatric Assessment (CGA), and compared these instruments with the VES-13. The Authors found that elderly patients with a VES-13 score ≥3, ECOG-PS score ≥1 or a KPS score ≤80% may have alterations on the CGA and should be referred to a geriatric-oncologist in order to identify geriatric problems that may negatively impact the survival [59].

One of the most used comorbidities assessment scale is represented by the Charlson Comorbidities Index (CCI), which is characterized by 19 items covering the most common comorbidities in elderly patients. Patients with GBM and CCI < 3 has a longer OS (22.0 months) than those with CCI ≥ 3 (10 months) [60]. Similarly, Ening et al have demonstrated in 233 newly-diagnosed GBMs that CCI could be an additional prognostic parameter for stratification in the preoperative setting [61].

Lorimer et al have conducted a survey to identify the main factors influencing clinicians in prescribing antineoplastic treatments following surgery in elderly GBM patients. The study revealed that clinicians consider of utmost importance clinical evaluation (KPS and comorbidities), radiological characteristics (tumor size) and family support rather than age, MGMT methylation status or availability of clinical trials [62]. Recently, the Elderly Task Force of the European Organization for Research and Treatment of Cancer (EORTC) has proposed a minimal dataset to better evaluate elderly population in daily clinical practice and clinical trials. This dataset includes CCI, IADLs, G8 geriatric assessment screening tool, and social situation, but needs to be validated in prospective cohorts.

5. Surgery in elderly GBM patients

Few studies have assessed the role of surgery in elderly glioma patients, and most of them are focused on GBMs. The aims of surgery in elderly patients are similar to younger patients: to obtain a histological and molecular diagnosis, perform a debulking and collect tissue for research. In parallel, neurosurgeons must preserve neurological status to avoid that postoperative neurological deficit will affect negatively the choice of adjuvant treatments. Different intraoperative techniques are available to optimize the resection and reduce postoperative neurological deficits, including neuronavigation, intra-operative monitoring and 5-aminolevulinic acid (5-ALA).

Cloney et al retrospectively analyzed the correlations between frailty and postoperative complications in a cohort of GBM patients aged ≥ 65 years using the Canadian Study of Health and Aging Modified Frailty Index (FI). Frailer patients received less aggressive surgery, had longer hospitalization, and experienced more complications, suggesting that FI could be a useful tool to predict the risk of postoperative complications [63].

The EOR has been demonstrated to significantly matter in elderly population. One prospective study only has been performed to investigate the role of EOR in 23 GBM aged > 65 years. The Authors defined as GTR when no enhancement of tumor was found in the post-operative scan as compared with STR when an enhancing residual tumor was less than 30%, and partial resection/biopsy when residual enhancing tumor was more than 30%. A prolonged OS was achieved in patients treated with GTR/STR (171 days, IC95% 146-278) as compared to those with biopsy (85 days, IC95% 55-157; p 0.035) [64]. Chaicana et al retrospectively analyzed 205 GBM patients aged ≥ 65 years, who underwent GTR/STR (133 patients) or biopsy (72 patients). GTR, STR, and biopsy were considered when > 99%, 90-99%, and <90% of tumor was removed, respectively. The Authors reported that patients tolerate GTR/STR without an increase of surgery-related morbidity and derive a prolonged OS (5.7 months) as compared with those treated with biopsy (4.0 months, p 0.02). Moreover, in patients aged ≥ 70 years the median OS was 4.5 months for 26 patients who underwent GTR/STR as compared with 3.0 months for 26 patients who underwent biopsy (p = 0.03) [65].

A retrospective German study, that analyzed prognostic factors in 103 elderly patients with GBM, concluded that the most important predictor of outcome was the EOR, with an OS of 2.2, 7.0 or 13.9 months for patients who underwent biopsy, STR or GTR, respectively [66]. Similarly, the NOA-08 trial reported that the EOR was the sole independent prognostic factor for survival [26]. Last, Perry et al displayed that patients with biopsy only had shorter PFS (HR 1.45; 95% CI 1.20-1.75; p<0.001) and OS (HR 1.67; 95% CI 1.38-2.02; p< 0.001) than those with STR or GTR [27]. In general, in the aforementioned studies, surgery was considered complete when no residual contrast-enhanced (CE) tumor was found on the postoperative MRI, without considering the residual non contrast-enhanced (NCE) lesion.

Scott et al reported that 46% only of GBM patients aged > 70 years underwent surgery plus radiotherapy among a cohort of 2836 patients [67], suggesting that in clinical practice there is a non-negligible tendency to prescribe supportive care rather than multimodal antineoplastic treatments with the increase of age [68]. Recently, Molinaro et al have suggested that the surgical plan may change based on the age of patients. The resection of the CE tumor was associated with prolonged OS in newly-diagnosed GBM. Moreover, the resection of CE plus NCE lesion was correlated with better OS in only ≤ 65 years patients with IDH wild-type GBM, regardless of the MGMT status [69].

6. Post-surgical treatments in elderly GBM patients

In 2005, Stupp et al published the results of a phase III multicenter, double-blind, placebo-controlled trial on 573 patients who received either radiotherapy (RT) or RT with concomitant daily TMZ followed by 6 cycles of adjuvant TMZ (so called “chemoradiation”). The trial showed an increase of median OS from 12.1 months to 14.6 months and 2-year OS improvement from 10.9% to 27.2% for patients receiving chemoradiation [24]. Moreover, MGMT methylated patients have longer OS (23.4 months) compared with unmethylated patients (12.6 months), suggesting a predictive value of MGMT methylation status [24,70]. The Stupp regimen is now considered the standard of care in GBM patients following surgery. However, a subgroup analysis of the Stupp trial, confirmed a benefit in OS for chemoradiation in comparison with RT alone in patients aged 61-65 years (12.2 months vs 11.4 months, respectively; HR 0.64; p 0.02), but did not find a

similar survival advantage in patients aged 66-70 years (10.9 months versus 12.0 months respectively; HR 0.78; p 0.29).

Some trials have specifically addressed the issue of the optimal adjuvant therapy in elderly patients. The ANOCEF Group have investigated the efficacy and tolerability of RT alone compared with supportive care in 81 GBM patients aged > 70 years, but the study was discontinued at the first interim analysis because of the significant benefit in OS of RT alone (29.1 weeks) in comparison with supportive care (16.9 weeks; HR 0.47; IC95% 0.29-0.76; p 0.002) without a negative impact on quality of life [71]. Rao et al compared in a prospective cohort a conventional RT schedule (60 Gy/30 fractions) with a short-course RT (40 Gy/15 fractions). The study showed no significant differences in OS (5.1 months versus 5.6 months, respectively; p 0.988) between conventional and short-course RT [72]. Later, a phase III randomized trial has investigated a further shortening of RT duration by comparing the schedule of 40 Gy/15 fractions in 3 weeks with a short-course RT of 25 Gy/5 fractions in 1 week. The Authors reported no significant difference in terms of PFS (4.2 months versus 4.2 months, respectively; p 0.716) and OS (7.9 months versus 9.6 months, respectively; p 0.988) [73]. Given the challenges in recruiting in such a trials, the sample size was limited (100 patients [72] and 98 patients [73], respectively), and primary outcomes are reflective to be lesser power. For instance, the Roa trial [72] was initially powered for equivalence, but the accrual was less than half of planned participants, thus closed the enrollment early without demonstrating the equivalency between standard and hypofractionated RT. The NORDIC trial has shown that in patients > 70 years the OS was prolonged with either standard TMZ or hypofractionated RT in comparison with standard RT (HR for TMZ vs standard RT 0.35; 95% CI 0.21-0.56; p < 0.0001; HR for hypofractionated vs standard RT 0.59; 95%CI 0.37-0.93; p 0.02). Patients treated with TMZ, who had MGMT promoter methylation, experienced a significantly longer survival than those without MGMT promoter methylation (9.7 months; 95%CI 8.0-11.4 vs 6.8 months; 95%CI 5.9-7.7; HR 0.56 [95% CI 0.34-0.93], p 0.02), while no difference was observed between patients with methylated or unmethylated MGMT promoter when receiving RT (HR 0.97 [95% CI 0.69-1.38]; p 0.81) [25]. The NOA-08 German trial has investigated in 373 elderly patients with GBMs and anaplastic astrocytomas the impact of **metronomic** TMZ versus standard RT: median OS was 8.6 months (95% CI 7.3-10.2) in the

TMZ arm compared with 9.6 months (95% CI 8.2-10.8) in the RT arm (HR 1.09; 95%CI 0.84-1.42; p 0.033). Also, in this study MGMT promoter methylation emerged as a predictive factor for response to TMZ [26].

Minniti et al have preliminarily suggested in a single arm phase II trial the efficacy and safety of chemoradiation with an hypofractionated RT course for elderly newly-diagnosed GBM [74]. In a similar patient population, Perry et in a phase III trial confirmed that a short course radiation (40 Gy/15 fractions) associated with concomitant and adjuvant TMZ resulted in an improvement of OS compared with radiotherapy alone (median OS 9.3 months vs. 7.6 months, respectively), as well as of median PFS (5.3 months vs. 3.9 months, respectively) [27]. MGMT methylated patients derived the major benefit in OS from short-course chemoradiation (median OS 13.5 months versus 10.0 months for unmethylated MGMT patients). Lastly, the survival advantage has been achieved without quality of life worsening and with manageable chemotherapy-related toxicities. The Perry trial enrolled patients with good performance status (ECOG 0-1 78.6% of patients) and cognitive status (median MMSE 27), and a high extent of resection (68.3%). Thus far it is unknown whether the short-course chemoradiation may be active as well in frail elderly patients or in those with poor performance status. Overall, the Perry schedule has shown a non-inferior efficacy compared to Stupp protocol for treating newly-diagnosed GBM, thus should be proposed for elderly patients in daily clinical practice, especially in patients with methylated MGMT promoter.

A single-arm, phase 2 trial (UKT-03) assessing lomustine-TMZ combination therapy for patients with newly-diagnosed GBM found a signal of improvement in OS for patients with methylated MGMT promoter [75]. The phase 3 CeTeG/NOA–09 trial has investigated whether the lomustine-TMZ plus RT might be superior to TMZ and RT in newly-diagnosed GBM with methylation of the MGMT promoter. Median OS was improved from 31.4 months (95% CI 27.7–47.1) with TMZ alone to 48.1 months (32.6 months–not reached) with lomustine-TMZ. The median age of patients was 50 years and no further investigation has been conducted in elderly population thus far [76].

A recent meta-analysis has evaluated 12 randomized clinical trials (RCTs) including 1818 elderly GBMs: six were conducted exclusively among elderly people aged ≥ 65, while the other 6 reported data for an elderly subgroup among a broader age range of participants. Overall, OS was prolonged in patients treated with chemoradiation compared with RT alone (HR 0.67, 95%CI 0.56-0.80) or TMZ alone (HR 1.42; 95%CI 1.01-

1.98). Poor evidence of efficacy of bevacizumab has been reported in association with chemoradiation for patients ≥ 65 years (HR 0.83, 95% CI 0.48-1.44) [77] by the phase III trials AVAGlio and RTOG-0825 [78,79]. The randomized, open-label, phase II ARTE trial compared hypofractionated RT (40 Gy/15 fractions) alone or associated with bevacizumab 10 mg/kg every 2 weeks in 75 patients aged ≥ 65 years. Median PFS was longer in the combined treatment in comparison with RT alone (7.6 and 4.8 months, p 0.003), but OS was similar (12.1 and 12.2 months, p 0.77). Median deterioration-free survival from baseline was 5.7 months in bevacizumab plus RT arm and 2.8 months in RT alone. Moreover, among 34 patients, who were on steroids at study entry, 21/22 patients (95%) in bevacizumab plus RT arm and 8/12 patients (66%) in RT alone arm interrupted steroids before progression [80]. In conclusion, bevacizumab does not confer any advantage in OS, but there is a benefit in terms of reduction of steroids and quality of life [81].

The locoregional alternating electric fields treatment (TTFields device) has been investigated in newly diagnosed GBM in the EF-14 trial, and reported encouraging results when associated with chemoradiation in terms of PFS (7.1 months) and OS (19.6 months) compared with chemoradiation alone (PFS 4.0 months; OS 16.6 months) [82]. One study only, using multivariate analysis, reported that TTFields device, when associated with conventional RT 60Gy/30 fractions plus concomitant and adjuvant TMZ in a cohort of GBM patients aged ≥ 65 years, leads to a median OS of 17.4 months (95%CI 9.0-31.5 months) compared with an OS of 13.7 months (IC95% 7.6-24.8) of RT/TMZ group [83]. Ongoing clinical trials on elderly patients with malignant gliomas are reported in Table 1.

7. Issues regarding lower-grade gliomas in elderly patients

LGGs occur preferentially in young adults with a median age of 41 years (range 35-44) [84]. The patients aged > 60 years represent a small percentage of LGGs (13.6%) [85], thus there are few data on patient selection and treatment strategies in this specific population. In general, the age is considered one of the most important prognostic factors in terms of OS in LGGs. Shomas et al retrospectively analyzed a cohort of 32 patients aged > 55 years with LGGs reporting a poorer prognosis (median OS of 2.7 years) than that of younger patients (median OS 13 years) [86]. Kaloshi et al retrospectively evaluated clinico-radiological characteristics and outcome of 62 LGG patients aged > 60 years: elderly patients had a lower performance status, larger tumor on MRI and lower rate of resection, resulting in a poorer OS (OS-5year of 40%

compared with 80% of younger counterpart) [87]. Another retrospective study reported in 20 patients aged ≥ 60 years that 25% died within 6 months and another 25% was alive at 27 months from the diagnosis; conversely, the third quartile of patients experienced more than 5-year survival, suggesting that a small subgroup of older patients with LGG may have comparable PFS and OS as younger patients [88].

Some prognostic scales have been developed to predict survival outcome in LGGs, but the cut-off of the median age used to assign the score was -/+ 40 years [89,90] or -/+ 50 years [91]. Similarly, the EORTC has validated a prognostic scale of 6 items (age, presence of neurologic deficits, MMSE score, histology, preoperative tumor size, tumor crossing the midline) in 203 patients (100 patients < 40 years and 103 patients ≥ 40 years) that underwent radiotherapy. Notably, the multivariate analysis showed that tumor size and MMSE were significant predictors of OS, suggesting that cognitive status could play a remarkable role in the tolerability of RT [92].

There is a limited number of studies that have investigated the role of EOR in older LGGs patients, and most of them did not include patients who were treated with aggressive surgery. Shomas et al reported in a series of 32 patients with a median age of 61 years that 2 patients only underwent a gross-total resection with a median OS of 3 years, versus 2.2 years in those (16 patients) who received biopsy alone [86]. Similarly, Kaloshi and Morsched series reported a low rate of gross-total resection (27% and 30.8%, respectively) [87,93], as well as Pouratian et al described in his cohort of 20 patient aged ≥ 60 years that 75% of patients were treated with biopsy and one patient only underwent gross-total resection [88]. Overall, the small number of patients treated with aggressive surgery in these studies does not allow any meaningful conclusion on the relationship between EOR and survival.

The phase III RTOG 9802 trial has demonstrated the benefit of the RT plus procarbazine/CCNU/vincristine (PCV) in terms of PFS and OS in 251 high risk LGGs (median age 40 years) [94]. However, a not negligible proportion of long term survivors may be affected by cognitive impairment after 8-12 years following RT [95,96], and this negative effect may be more pronounced in elderly LGGs. TMZ has been suggested as an up-front treatment in order to delay RT and the risk of neurocognitive dysfunctions in 2 phase II trials and in the phase III EORTC 22033-26033 trial [97,98]. In this regard, the aim of the study was to investigate whether the dose-dense TMZ was superior to standard radiation therapy in high-risk LGGs. No difference in

median PFS was observed between the two arms (TMZ arm: 39 months; 95% CI 35-44; RT arm: 46 months; 95% CI 40-56; HR 1.16; 95% CI 0.9-1.5, p 0.22). For patients with IDH 1/2 mutation and 1p/19q codeletion outcomes were similar (TMZ arm: 55.0 months; RT arm: 61.6 months). However, for patients with IDH 1/2 mutation and absence of 1p/19q codeletion median PFS was longer for those receiving RT (55 months, 95% CI 48-66) compared to TMZ (36 months, 95% CI 28.4-47; HR 0.53; 95% CI 0.35-0.82; p 0.0043) [99]. These results suggest that RT may be superior to chemotherapy in astrocytomas. Data on OS are not yet mature. Overall, it is still unknown which is the optimal treatment (RT plus chemotherapy or chemotherapy alone) in elderly patients with LGGs. One should have in mind that chemotherapy does not completely avoid the risk of cognitive deficits as may cause acute and short-term cognitive side effects [100], as well as long-term changes in cognitive functioning (the so-called "chemo-brain") [101,102]. Some preclinical data have shown that chemotherapy may damage the CNS white matter leading to an aberrant myelination which is comparable to that observed following RT [103]. Reversible encephalopathy (delirium) may represent the symptom of such a CNS damage, or may be caused by other factors, such as systemic infection, metabolic changes, or drug interactions. Last, seizures and antiepileptic drugs have a significant impact on cognitive functions [104] and may interact with chemotherapy. In general, non-inducers antiepileptic drugs, such as levetiracetam and lacosamide, are to be preferred to avoid drug interactions and adverse events, particularly in elderly population with significant comorbidities. Corticosteroids are largely used to control tumor edema, but may increase the risk of osteoporosis, bone fracture, myopathy, and diabetes mellitus. Dexamethasone is the most frequently administered drug, with a potent glucocorticoid activity but low mineralocorticoid effect, which avoids alterations of blood electrolyte levels. Furthermore, because of its long biological half-life, a single daily administration is sufficient. Mantilla et al has reported that prolonged use of steroids in glioma treatment can lead to adrenal insufficiency (AI) and subsequent steroid dependence due to suppression of the hypothalamic-pituitary-adrenal axis. The risk of AI is increased with high dose (8 mg/day) and long duration of treatment (> 8 months) [105]. In general, the lower effective dose of dexamethasone for a limited period would be recommended to control brain edema and reduced side effects.

8. Expert opinion

Elderly patients with glioma have special needs and a holistic evaluation is mandatory to offer the optimal treatment. Different biological, clinical, and lifestyle factors may play a role in determining the survival of elderly patients, but the current prognostic scales are far to be exhaustive. Biological age, KPS, and residual tumor following surgery are factors mostly used to select candidates for adjuvant treatment in daily clinical practice, but do not always reflect the heterogeneity of elderly glioma patients. The absence of standardized scales tailored to elderly patients with glioma leads to a choice regarding type or regimen of antineoplastic treatments based mainly on physician's and/or patient's preference. The CCI covers a large spectrum of medical comorbidities, that influence survival and tolerability to antineoplastic treatments. Importantly, the CCI is continuously updated: for example, the presence of COVID-19 infection has been recently added as a risk factor of frailty in the elderly. However, the CCI does not consider the presence of mood disorders and the daily living skills of the patient, therefore an integration with the VES-13 and/ or GDS would be useful in selecting the fit patients for antineoplastic treatments. An integration of additional items, such as presence of seizures, need for corticosteroids or antiepileptic drugs, IDH 1/2 mutations, is needed to better predict the tolerability of treatments and outcome. A neurocognitive assessment to monitor cognitive functions must be provided to better balance between benefit and adverse events from antineoplastic treatments. In this regard, the EORTC questionnaires (QLQ-C30 and BN20, EQ-5D), which are used in most of RCTs, fail to capture the specific needs of elderly population. Moreover, they do not measure cognitive performances in daily activities and their implication in daily life functioning. Therefore, new tailored questionnaires should be designed and validated in prospective cohorts.

Which conclusions can be drawn on the management of GBM? Based on available data, when feasible and in presence of a good performance status and lack of major comorbidities, GTR should be attempted in elderly patients with GBMs without considering advanced age as a contraindication. For fit patients aged between 65 to 69 years, both Stupp (60 Gy/30 fractions) and Perry (40 Gy/15 fractions) regimens can be proposed, with similar efficacy and tolerability. Conversely, for patients aged ≥ 70 years, the Perry schedule should be preferred, particularly in MGMT methylated patients, to shorten the treatment time. For unfit and frail patients, TMZ alone when MGMT is methylated or hypofractionated RT alone when MGMT is

unmethylated, are the optimal choice (Fig.1). It will be of utmost importance for the coming years to better define molecular and clinical characteristics that allow to subdivide elderly patients with gliomas into well defined prognostic subgroups in light of the development of new tailored treatment strategies, such as targeted agents or immunotherapy.

The management of elderly LGGs raises several issues. Few data are available regarding the benefit of an extensive resection in terms of OS in LGGs aged ≥ 65 years. Considering that patients with similar age and HGGs undergo, when feasible, an extensive resection with acceptable postoperative outcomes, we may argue that such an aggressive surgery should be performed in older patients with LGGs. Furthermore, the value of EOR could be more important in patients with mild-patchy enhancing LGGs, underlying an initial malignant transformation, whose diagnosis is relevant for the design of postoperative management.

As most of IDH mutated and 1p/19 codeleted oligodendrogliomas, and IDH mutated non 1p/19q codeleted astrocytomas have a methylated MGMT promoter [106], the use of TMZ as up-front chemotherapy has been suggested as an effective treatment in order to avoid or delay the radiotherapy-related neurotoxicity in elderly patients. A recent reevaluation of EORTC 22033 trial has reported that the use of a score that reflects the extent of MGMT methylation is a predictive factor when using TMZ, especially in oligodendrogliomas [107]. However, these results need to be validated in prospective datasets. Furthermore, data regarding long-term cognitive preservation following either TMZ or radiotherapy are missing. The challenge in the coming years is the identification of molecular pathways, that drive tumor progression and are druggable with good tolerability. Up to date, inhibitors of IDH mutations seems to be the most promising [108]. However, only well designed clinical trials focused on elderly patients with LGGs will be able to define the optimal sequence and combination of therapy.

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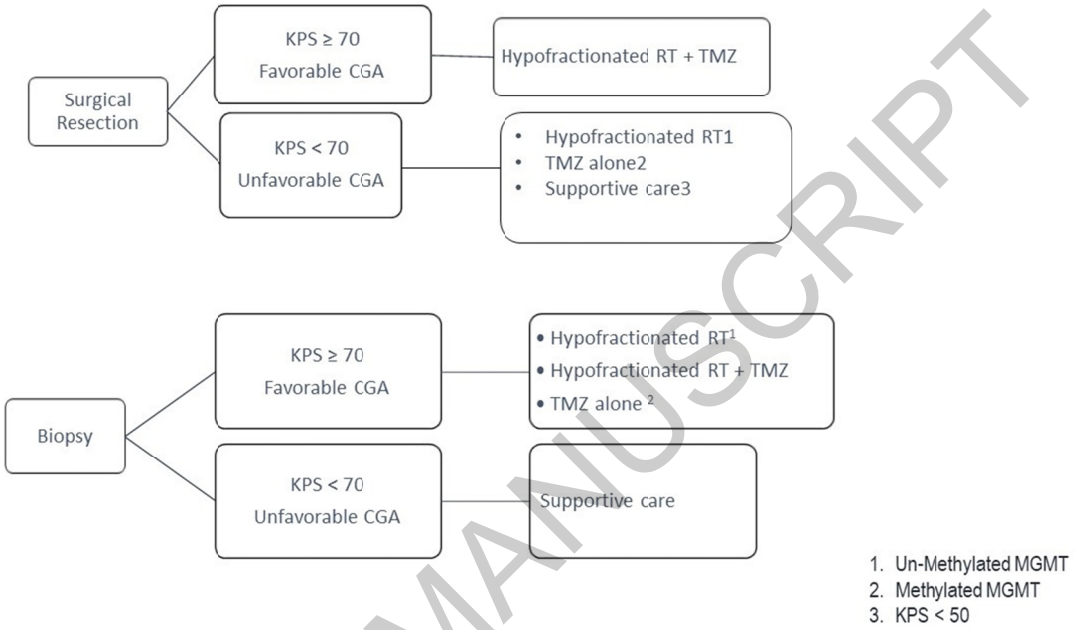

Figure 1

Table 1. Current randomized clinical trials in elderly patients with malignant glioma (from https://clinicaltrials.gov updated on May 2020)

Trial	Phase	N° of patients	Histology	Treatment arms	Endpoints
STEAM trial NCT03224104	1	81	Newly-diagnosed or first recurrence of grade III AA or GBM in patients > 65 years	• Group A: newly diagnosed grade III AA/GBM MGMT unmethylated who will receive TG02 + hypofractionated RT • Group B: newly-diagnosed grade III AA/GBM MGMT methylated who will receive TG02 + TMZ • Group C: first relapse of grade III AA/GBM previously treated with Stupp regimen who will receive TG02 alone	Primary: - MTD - PFS at 6 months Secondary: - PFS - OS - Best overall response rate (PR+CR) - Toxicity (CTCAE version 4.0) - Molecular markers (MYC, MCL-1, CDK9/CDK5)
NUTMEG trial NCT04195139	2	102	Newly-diagnosed GBM > 65 years	• Group A: TMZ 150-200 mg/m^2 day 1-5 every 28 days for 6 cycles plus Nivolumab 240 mg every 2 weeks for cycles 1-4, then 480 mg every 28 days cycles 5-6 • Group B: TMZ alone	Primary: - OS Secondary: - PFS - Toxicity - Health related quality of life (EORTC questionnaires) - Neurological status (NANO criteria) - Response rate (modified RANO and iRANO)
GERAS trial NCT04218019	2	68	Newly-diagnosed GBM > 70 years	• Group A (early TTFields): hypofractionated RT +/- TMZ (according to the standard and local physician's decision) • Group B (late	Primary:: - SCRT Secondary: - Toxicity (CTCAE version 5.0) - PFS

				TTFields): hypofractionated RT +/- TMZ + TTFields treatment which start 4 weeks after the end of RT	- Health related quality of life (EORTC questionnaires)
NCT01602588	2	54	Newly-diagnosed GBM > 70 years	• Group A: short-course RT + hydroxychloroquine 200 mg bd from 14 days post surgery until clinical and/or radiological progression • Group B: short-course RT alone	Primary: - OS at 1 year Secondary: - Toxicity
NCT01149850	2	50	Newly-diagnosed GBM > 70 years	• Single arm: BEV 10 mg/kg every 2 weeks on day 1-5, then every 28 days fro 24 courses associated with conventional RT + TMZ	Primary: - OS at 2 years Secondary: - PFS at 2 years
NCT01985087	1/2	40	Newly-diagnosed GBM > 70 years	• Single arm: hypofractionated RT (3.4 Gy for consecutive 5 days for 2 weeks) + TMZ	Primary: - Toxicity Secondary: - OS - Quality of life (Fact-BR assessment)

AA: astrocytoma; GBM: glioblastoma; MGMT: O-6-methylguanine-DNA methyltransferase; TG02: zotiraciclib; RT: radiotherapy; TMZ: temozolomide; TTF: Tumor-Treating Fields device; BEV: bevacizumab; MTD: maximum tolerate dose; PFS: progression-free survival; OS: overall survival; PR: partial response; CR: complete response; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; NANO: Neurologic Assessment in Neuro-Oncology; RANO: Response Assessment in Neuro-Oncology; iRANO: immunotherapy Response Assessment for Neuro-Oncology; Fact-BR: Functional Assessment of Cancer Therapy for BRain