Assessment and treatment relevance in elderly glioblastoma patients

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Epidemiology
Glioblastoma (GBM) is the most common malignant primary brain tumor. Its incidence has increased and will continue to increase, particularly because the older segment of the world population is growing faster than any other age group.1

Oncological care management for elderly GBM patients still constitutes real challenges for multidisciplinary teams.2 Most clinical studies exclude elderly patients,3,4 and standards of care do not exist for GBM patients aged >70 years.5 This explains the great variability in oncological care patterns for elderly GBM patients in different countries and across regions. Moreover, elderly GBM patients are often (but not always) characterized by a high rate of associated morbidity, which, could also limit the choice of therapeutic options and explain, at least in part, why elderly GBM patients have been undertreated until recently.6–8

The goal of this paper is to review (i) epidemiology; (ii) tumor biology/molecular factors; (iii) the relevant spontaneously and therapeutic prognostic factors and their assessments; (iv) classic and elderly-specific endpoints; and (v) recent and ongoing clinical trials for elderly GBM patients. This work includes perspectives and personal opinions on this topic.

Epidemiology

In the United States, GBM incidence-adjusted rates for all patients, for patients aged 65–74 years, and patients aged 75–84 years are 3.2, 13.2, and 14.6 per 100 000 person-years, respectively.9 In population-based studies, median age at the time of diagnosis was 64 years.10 GBM incidence has increased and will continue to increase, in fact nearly half of GBM patients are aged ≥65 years, and more than a quarter of cases are patients aged >70 years.11,12 and by 2050, the percentage of persons aged >65 years worldwide is expected to increase by 238%.1

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Survival data from population-based studies dedicated to elderly GBM patients are very rare and do not generate enough detailed prognostic factors and treatments to determine the best medical approach for this population group. However, in the United States, median survival (MS) rates of all adult patients with GBM were 8.1 months in the period 2000–2003 (pre-temozolomide [TMZ]) and 9.7 months in the period 2005–2008 (post-TMZ). The MS rate was 4 months for elderly GBM patients (aged ≥65 years) during the period 1994–2002. For elderly GBM patients (aged 70–79 years) treated with at least surgery and radiotherapy (RT), MS was 7.9 months in the period 2000–2003 and 9.3 in the period 2005–2008.

Tumor Biology and Molecular Factors

The poor prognosis for elderly GBM patients could be explained by (i) the percentage of frail patients; (ii) the percentage of under-treated patients; and (iii) intrinsic biological specificities and different molecular patterns. The prognostic effects of TP53 mutation, epidermal growth factor receptor (EGFR) amplification, CDKN2A/p16 alterations, and loss of chromosome 1p are age-dependent. It was emphasized that age should be taken into account because patients with TP53 mutation were younger at diagnosis compared with those without TP53 mutation (P = .05). TP53 alterations were associated with reduced survival in patients aged >70 years, whereas the opposite was seen in their younger counterparts. In the same way, EGFR amplification had negative prognostic values in younger patients versus positive prognostic values in older patients (for review, see). These findings suggest that GBM molecular pathways may differ in elderly patients.

Besides the previous results, meaningful information was obtained from the classification of GBM with regard to gene expression signature. At least 4 distinct expression signatures have been identified: classical, mesenchymal, neural, and proneural. Abnormally high levels of EGFR and lack of p53 mutation characterize classical GBM, which exhibits the best survival in response to aggressive treatments. The proneural signature confers significantly longer survival compared with other gene expression-based subtypes. Retrospective analyses found that the survival benefit of younger patients was nullified when patients were stratified according to their gene expression group. In fact, elderly patients rarely exhibit proneural gene expression signature.

It has been suggested that alternative lengthening of telomere (ALT) mechanisms were present in 15% of GBM patients. ALTs were frequently accompanied by isocitrate dehydrogenase 1 (IDH1) mutations and were associated with longer survival that was independent of age or treatments.

Up to now, only 2 main prognostic biomarkers have been used for GBM in clinical practice: methylguanine methyltransferase (MGMT) promoter methylation and IDH1/2 mutation status. MGMT promoter methylation was validated as a major prognostic factor for patients with GBM in the EORTC/NCIC trial and confirmed in elderly GBM patients. In addition, data from 2 recently published prospective studies in elderly GBM patients showed that MGMT promoter methylation also seemed to predict response to TMZ. Several studies documented that mutations of IDH1/2 were associated with and genetically defined secondary GBM, which is associated with better overall survival (OS) regardless of treatment. The incidence of secondary GBM, however, decreases with age. In contrast to MGMT promoter methylation, IDH1/2 mutations are age-dependent and only rarely manifest as GBM in elderly patients (<2%).

Of course, treatments adapted to the biology of the tumor need biopsy or resection tissue samples.

Prognostic Factors and Assessment for Elderly Glioblastoma Patients

A recent retrospective recursive partitioning analysis study of GBM patients aged ≥70 years identified 4 prognostic subgroups with noticeably different MS rates: subgroup I, patients aged <75.5 years with resection; subgroup II, patients aged ≥75.5 years with resection; subgroup III, patients with Karnofsky Performance Status (KPS) from 70%–100% with biopsy; and subgroup IV, patients with KPS <70% with biopsy. MS rates for groups I–IV were 9.3, 6.4, 4.6, and 2.3 months, respectively using the US dataset and 8.5, 7.7, 4.3, and 3.1 months, respectively, using the French dataset. However, prognostic factors influence the probability of resection and oncological treatments. So we must determine which clinical, radiological, and biological factors are relevant in order to offer our patients the best oncological strategies in the framework of individualized care.

Spontaneous Prognostic Factors and Surgery

Age is one of the most important prognostic factors for all GBM patients. In the US Surveillance, Epidemiology and End Results (SEER) program, 18 registries between 1995 and 2009 showed the 2-year relative survival rates for GBM to be 20.6%, 14.2%, 6.9%, and 2.6% for patients aged 45–54 years, 55–64 years, 65–74 years, and >75 years, respectively. Many other factors influence survival for elderly GBM patients, such as KPS, neurological impairments, comorbidities, location of the lesion, methylation status, etc. There have been no prospective studies with precise multivariate analysis to define the importance of each factor. However, some retrospective studies are interesting to consider. For example, French data on GBM patients aged ≥70 years showed that the most significant clinical prognostic factor before surgery was the KPS (particularly KPS after corticoid treatment). In a recent multivariate analysis performed at the Mayo Clinic, younger age and single lesion were associated with better OS. In other studies, the following preoperative factors have been retrospectively associated with decreased survival in elderly GBM patients undergoing surgery: KPS <80%, chronic obstructive pulmonary disease, motor dysfunctions, language deficit, cognitive deficit, and tumor size >4 cm. Survival times ranged from 9.2 months (patients with 0 to 1 risk factors) to 4.4 months (patients with 4 to 6 of these risk factors).

It is particularly important to determine the real risk of surgical complications in elderly GBM patients because complications such as new neurological impairments are associated with decreased survival and decreased quality of life (QoL). Interestingly, the study by Tanaka et al. (105 patients, aged ≥65 years) documented a higher overall complication rate for patients undergoing biopsy than for those undergoing resection (30.8% vs 18.9%), although the difference did not reach statistical significance (P = .18). This included 9.6% with permanent neurological worsening, 17.3% with regional complications, and 9.6% with systemic complications. Clinically significant hemorrhage at the
tumor site was noted in 11.5% of patients undergoing biopsy
compared with 0% patients undergoing resection (P = .01). The
perioperative mortality rate associated with biopsy (within 30
days of surgery) was 7.7%, which almost reached statistical
significance in comparison with the rate of 0% in patients who
underwent resection (P = .06). Thus, complication rates for ster-
eotactic biopsy in this series of elderly GBM patients were higher
than those reported in large unselected stereotactic biopsy
series. These higher rates likely reflect both the type of lesions
chosen for biopsy (deep eloquent locations in which even minor
postoperative edema or hemorrhage can have major conse-
quences) and the elderly patient population.

From the authors’ neurosurgical point of view, the choice of re-
section versus biopsy is based mainly on the topography of the
tumor and its resectability, mass effect, and limited infiltration.
In our personal experience, we do not have a cut-off age for pro-
posing resection in these cases if the patient has a healthy status
and limited risk of comorbidities with KPS \( \geq 70\% \) and Mini-Mental
State Examination (MMSE) \( \geq 25\% \). Generally, we discuss each pa-
ient’s case in multidisciplinary meetings in order to assess, in a
collateral manner, the advantages and disadvantages of resec-
tion/biopsy/palliative care in context, possibly proposing (or not)
adjuvant treatment after surgery.

**Radiotherapy**

Standard treatment after tumor resection or biopsy includes
postoperative fractionated radiotherapy (RT), classically 60 Gy in
30 fractions for GBM patients aged \( \leq 70\) years. For elderly GBM
patients, however, the optimal RT schedule still remains to be
determined, and several different studies have shown significant
results. The effect of RT (total dose, 50 Gy; daily, 5 days per week,
8 Gy) in high-grade gliomas has previously been demonstrated
and validated in elderly patients (aged \( \geq 70\) years) with KPS
\( \geq 70\% \). In the study by Keime-Guibert et al., 85 patients were
randomly assigned to receive supportive care only or supportive
care associated with RT. Patients in the RT group showed an
improved MS (29.1 weeks vs 16.9 weeks; P = .02) with no negative
impact on QoL. The efficacy of RT in elderly patients has been con-
firmed in a population-based study on 2836 GBM patients aged
\( \geq 70\) years, regardless of their performance status; the population
was identified from the SEER registry in the United States. In the
Nordic Clinical Brain Tumour Study Group phase III clinical trial
(patients aged \( \geq 60\) years, WHO performance status 0–2), the MS
of patients treated with standard RT (60 Gy administered in 2 Gy
fractions over 6 weeks) was 6 months. In another phase III study
in patients aged \( \geq 65\) years (with a KPS \( \geq 60\% \)) comparing che-
motherapy (CT) with TMZ and standard RT, the MS in the RT group
was 9.6 months. Other studies have investigated the optimal
course of RT between the standard schema (60 Gy in 30 fractions
over 6 weeks) or hypofractionned RT. Rao et al. conducted a
prospective, randomized clinical trial that successfully proved
the noninferiority of an abbreviated RT course (40 Gy in 15frac-
tions over 3 weeks) in elderly GBM patients (aged \( \geq 60\) years;
KPS \( \geq 50\% \)). In this study, 10% of patients in the hypofractionated
RT group, compared with 25% in the standard RT group, had to
stop the treatment prematurely, suggesting a better tolerability
for the abbreviated course. In the Nordic study, patients treated
with standard RT had a lower survival compared with those treat-
ed with TMZ, but there was no difference between the group of
patients treated with a hypofractionated course of RT and the
TMZ group (P = .12). For patients aged \( > 70\) years, survival was
significantly better in the hypofractionated RT group compared
with the standard RT group (P = .02).

On the other hand, few experimental and clinical studies have
shown that ultrafractioned RT, delivering low doses (<0.75 Gy)
survival, could be effective for GBM patients even for
those aged \( \geq 70\) years. A large variety of irradiation treatment
protocols has been used with different total doses, sizes, and
numbers of fractions. Because of the low repair capacity of the
normal brain, the biologically effective dose, rather than the
“physical” irradiation dose, should be considered when analyzing
of irradiation protocols.

Overall, some questions remain unanswered regarding RT for
elderly GBM patients. For example, the impact of postoperative
RT has yet to be proven beneficial when several poor prognostic
factors (eg, low KPS, neurocognitive or motor dysfunctions,
large tumor size) are present concomitantly in elderly patients.
Moreover, RT requires daily trips to the hospital and results in in-
creased fatigue, which should consider when we propose RT to
frail patients.

**Chemotherapy**

The oral formulation and tolerability, in addition to clearance
independence of renal or hepatic function, have made TMZ a very
acceptable drug for elderly patients. Generally, <10% of patients
developed Common Toxicity Criteria grade 3 or 4 hematologic
toxicity, and <2% of patients had to stop treatment due to ad-
verse events. In a recent, nonrandomized phase II trial, TMZ
showed acceptable tolerance in frail elderly GBM patients (KPS
\(< 70\%\)). It was associated with functional status improvement
in 33% of patients and appeared to increase survival compared
with best supportive care alone, especially for patients with meth-
ylated MGMT promoter. The German study, NOA-08, randomized
373 patients aged \( > 65\) years with newly diagnosed anaplastic astrocytoma or GBM and a KPS \( > 60\% \) to either stan-
dard RT alone (60 Gy in 30 fractions) or single-agent TMZ (dose-
dense schedule). MS was 8.6 months in the TMZ group (see recent
and ongoing clinical trials paragraph for more details). Yin et al.
published a meta-analysis that systematically evaluated TMZ
monotherapy in older GBM patients. Studies comparing TMZ ver-
sus RT in elderly patients (aged \( \geq 65\) years) with newly diagnosed
GBM were eligible for inclusion. Only 2 randomized clinical trials
and 3 comparative studies were included in the analyses, which
revealed an OS advantage for TMZ compared with RT. However,
a sensitivity analysis of 2 randomized clinical trials only supported
its noninferiority. Most elderly patients tolerated TMZ despite an
increased risk of grade 3–4 toxicities, especially hematological
toxicities. The QoL was similar between the groups. In patients
with methylated tumors, TMZ was more beneficial than RT
alone for improving OS. It was concluded that MGMT testing
might be helpful for determining individualized treatment.

**Radiochemotherapy**

The landmark paper by Stupp et al. changed the standard of care
for patients with newly diagnosed GBM by demonstrating in-
creased survival for patients receiving RT with concurrent TMZ,
followed by adjuvant TMZ, compared with RT alone (MS, 14.6 vs
12.1 months; P < .001). However, this study excluded patients aged >70 years, and some skepticism remains about the use of TMZ in elderly patients despite its easy administration and relatively benign side-effect profile.47,48 Some recent papers have reported favorable survival for elderly GBM patients receiving RT and TMZ,49 such as 10.6 months with the Stupp regimen50 or 11 months with adjuvant RT and reduced TMZ dosage.51 While these MSSs are less than those in the Stupp study, the results must be interpreted in the context of the commonly reduced survival for older patients. The multivariate retrospective analysis study by Tanaka et al.32 also supported the notion that adjuvant treatment in elderly GBM patients was a strongly favorable prognostic factor. Among patients receiving adjuvant treatment, the addition of CT (mainly TMZ) to RT was associated with longer OS compared with RT alone in a univariate analysis (median OS, 11.5 vs 4.5 months; P = .01); however these results did not remain significant in a multivariate analysis (P = .27). Moreover, patients who received adjuvant treatment lived substantially longer when they had resection versus biopsy (MS, 11.5 vs 6.5 months). With maximal safe resection followed by the combination of RT and CT, median progression-free survival (PFS) and OS among elderly GBM patients (aged ≥65 years) were respectively 8 and 12.5 months; when limited to patients aged ≥70 years, the rates were respectively 8 and 11.5 months.32

In a meta-analysis of 16 nonrandomized studies (in the absence of a randomized study) of combined RT and TMZ in elderly GBM patients, Yin et al. concluded that combined RT/TMZ conferred a clear survival benefit for a selection of elderly GBM patients who had a favorable prognosis (eg, extensive resection, favorable KPS). Toxicities were more frequent but acceptable. Future randomized trials are warranted to justify a definitive conclusion.47

Comprehensive Geriatric Assessment: Evaluation of Older Patients

Among elderly cancer patients of the same chronological age, there is wide heterogeneity in physical and psychological functions. While some older patients tolerate and benefit from standard cancer treatments, others require dose reductions as well as delays and discontinuations of different therapeutic modalities. Comprehensive geriatric assessment (CGA) is a process developed by geriatricians to evaluate the functional and global health status of the elderly patient. The goals of CGA are identification and management of age-related problems, selection of the most appropriate therapy, and avoidance of futile therapy/over-treatment as well as undertreatment.52,53 CGA consists of a thorough evaluation of comorbid conditions, functional status, nutritional status, social support, polypharmacy, and cognition.52,54 CGA results are closely related to the prognosis of elderly patients in general. The process has also been found beneficial for assessing life expectancy, predicting treatment tolerance, and defining frailty for older cancer patients. Mortality at 2 years increases with lower functional status,55 dementia, and depression.56 Dependency in daily living activities, as measured by the Instrumental Activities of Daily Living (IADL) scale, poor nutritional status and lack of social support have been associated with a worse tolerance to CT.57

Recently, the Elderly Task Force (ETF) of the European Organisation for Research and Treatment of Cancer (EORTC) proposed a consensus for an elderly minimum dataset (MinDS),53 available at Annals of Oncology online: http://annonc.oxfordjournals.org/content/suppl/2010/11/08/mdq687.DC1/Appendix_ETF_CGA_dataset.doc) to be collected from older cancer patients. This proposed dataset includes the G8 questionnaire,58 IADL questionnaire,59 information about social situation, and the Charlson Comorbidity Index (CCI).60

The literature is limited regarding CGA in elderly GBM patients. Fiorentino et al. recently evaluated the Adjusted-Age CCI in the assessment of adjuvant radiochemotherapy for elderly GBM patients and showed that Adjusted-Age CCI influenced survival in both univariate and multivariate analyses (P = .004, P = .001, respectively). In a complementary work,62 the effectiveness and good tolerance of radiochemotherapy in elderly GBM patients was confirmed when KPS >70% and CCI <3. However, this study pooled data from 4 prospective phase II trials that included only elderly patients in good general health. Therefore, CGA should be developed in general clinical practice, and the multidisciplinary team managing the care of elderly GBM patients should include a geriatric physician. (This inclusion is mandatory at some institutions.)63

Imaging Data

Considering the elderly GBM patient subgroup, there is a crucial need for specific, noninvasive imaging biomarkers associated with OS and PFS, in fact morphological biomarkers, especially topography-related ones (e.g. superficial vs. deep, nonequivalent vs. eloquent) have been validated as relevant prognostic factors in GBM.32,64 There is a recognized association between GBM involving the subventricular zone and decreased OS and PFS.65 Tumor’s geometry and growth rate could be a valid method for assessing treatment response in discriminating OS and PFS following therapy for GBM.66 Proliferative volume, estimated by fluorothymidine PET, has been associated with OS in high-grade gliomas.67 Diffusion tensor imaging-derived measures have demonstrated correlation to aggressive histopathological features68 and seem to be otherwise promising biomarkers associated with OS,69 PFS,70 and MGMT promoter methylation status.71 Finally, new radiogenomic studies have associated MR imaging predictors to molecular profile and survival;72 for example, a new marker aggregating volume, age, and KPS has revealed an interesting link to prognostic microRNA gene signature.73

Classic and Specific Elderly Endpoints

Until recently, the “gold standard” for outcome measurement in most cancer clinical trials has been OS. However, OS might not be the most appropriate endpoint for many cancer patients, specifically those who are older53 (ie, elderly GBM patients).75 Other factors like QoL, maintenance of functional independence, absence of serious therapy-related side-effects, and burden of treatment are equally important considerations for the older population. Indeed, the issues of quantity versus QoL and maintenance of independence are fundamental for elderly patients. Participants in the ETF of the EORTC agreed that changes in social situation, functional status, and QoL should be measured and documented in all research involving older patients.53

Two approaches, composite endpoints or co-primary endpoints, were proposed for incorporating efficacy, QoL and toxicity measures as primary criteria when promoting the success of a
new therapeutic strategy. Trials based on composite endpoints would be declared successful if the new treatment yields an adequate trade-off between efficacy, QoL and toxicity; the drawback is that no statement can be formulated in terms of efficacy or toxicity or QoL separately. Trials based on co-primary endpoints would be declared successful if the new treatment is successful for each of the primary endpoints; the drawback is that more patients are needed for conducting such trials. Adaptive (Bayesian) trial design is also a useful design for studies in frail populations because the investigator can adjust procedures early-on to accommodate the data produced in the trial itself. 53

Recent and Ongoing Clinical Trials

Stummer et al. showed that tumor fluorescence derived from 5-aminolevulinic acid enables more complete resection of contrast-enhancing tumor, leading to improved PFS in patients with malignant glioma, but only a small number of elderly patients were included. 76 The only phase III trial randomly comparing debulking surgery versus biopsy followed 30 patients aged >65 years with high-grade gliomas. It showed that the survival rate was about 2.7 times longer after craniotomy (P = .049) but did not demonstrate any benefit in terms of neurological deterioration. 77 A trial entitled “Impact of surgery in the treatment of supratentorial malignant glioma patients >70 years” is still recruiting in France (http://www.sante.gouv.fr/IMG/pdf/results_PHRC_2006_cancer.pdf).

Although the role of RT plus concomitant and adjuvant TMZ treatment still remains uncertain for elderly GBM patients, few retrospective studies 16,78 have shown a beneficial effect of this management strategy after biopsy or resection. Fiorentino et al. 61 reported that the treatment was safe and effective in 35 patients aged >70 years with KPS >60%. Furthermore, a phase II study, performed in 71 patients aged >70 years with KPS >60%, showed that treatment with a lower dose of RT (40 Gy in 15 fractions over 3 weeks) plus TMZ as concomitant and adjuvant (12 cycles) was well tolerated and prolonged survival for these patients. 79

The Nordic Clinical Brain Tumour Study Group performed a phase III trial (342 GBM patients aged >60 years). 80 The study was a large, randomized trial of TMZ alone, short-course hypofractionated RT (34 Gy in 3.4 Gy fractions administered over 2 weeks) or standard 6-week RT of 60 Gy administered in 2 Gy fractions. The conclusion was that the GBM patients treated with standard RT over 6 weeks, especially those older than 70 years, had poor prognostic outcomes. These findings suggest that TMZ or hypofractionated RT over a 2-week period might be valid alternative strategies, and MGMT promoter methylation status might be a useful biomarker to help make treatment decisions.

The NOA-08 phase 3 trial enrolled 412 patients aged >65 years with confirmed anaplastic astrocytoma or GBM. 81 Patients were randomly assigned 100 mg/m² TMZ, given on days 1–7 of 1-week-on/1-week-off cycles, or RT of 60 Gy, administered over 6–7 weeks in 30 fractions of 1.8–2 Gy. MS was 8.6 months in the TMZ group versus 9.6 months in the RT group (P non-inferiority = .033). The authors concluded that TMZ alone was noninferior to RT alone in the treatment of elderly patients with malignant astrocytoma and that MGMT promoter methylation seemed to be a useful biomarker for outcomes by treatment and could be helpful in choosing the most appropriate therapeutic options.

These results are confounded in both studies by the high crossover rates between RT and TMZ due to the recurrence of disease. The poor RT results in the Nordic trial might be related to the study design rather than to biological reasons; therefore, a separate comparison of patients with MGMT promoter methylation in the TMZ and hypofractionated RT groups might alter these findings. 80 These 2 trials should encourage discussion on whether TMZ alone, with RT only as salvage, could constitute proper therapy for patients with MGMT promoter-methylated tumors.

The current National Cancer Institute of Canada and EORTC CE.6/26062/22061 randomized study of short-course RT, with or without concurrent and adjuvant TMZ, will help determine the optimal treatment, using currently available therapies, for this older cohort. 81 Holdhoff and Chamberlain recently made the following 2 following statements about this trial: (i) the study will provide clarity regarding the role of hypofractionated RT/TMZ versus single-modality RT, but it presupposes no added benefit in using 60 Gy RT in 30 fractions based on the earlier Canadian trial; and (ii) if RT alone is inferior therapy for elderly patients with methylated MGMT tumors, the question of whether this treatment might compromise survival is difficult to answer because the response based on MGMT methylation was never powered sufficiently to determine the answer unequivocally.

Besides the strategies already discussed, various exploratory noncomparative clinical trials have provided initial data suggesting that bevacizumab alone, or in combination with irinotecan, is active and has a manageable safety profile for patients with recurrent GBM. 82,83 The benefit and safety profile was validated in a randomized, noncomparative phase 2 trial (the BRAIN study; AVF3708g) in GBM patients following first or second recurrence after RT and TMZ. 84 The 2 phase II studies of bevacizumab in combination with TMZ and RT for patients with newly diagnosed GBM (AVAglio and RTOG 0825) did not exclude elderly patients. First results were recently presented (2013 American Society of Clinical Oncology (ASCO) Meeting): neither study showed an OS advantage, even if PFS was improved. 2 In addition, the results of another phase II study entitled “Bevacizumab and TMZ in treating older patients with newly-diagnosed GBM” (NCIT011 49850) will be published soon. Preliminary results were presented at the last ASCO meeting (June of 2013): the addition of bevacizumab to TMZ added no benefit to TMZ only. 85

Future Evaluation for Elderly Glioblastoma Patients

As already mentioned, endpoints of future clinical trials for elderly GBM patients should include OS, PFS, QoL, maintenance of functional independence, absence of serious therapy-related side-effects, and burden of treatment. Such clinical trials would be long and difficult to perform. In the near future, different drugs, successive treatments, and possibly different oncological strategies based on the tumor biological profiles will be developed for the care and management of elderly GBM patients (and, by extension, all central nervous system tumor patients). One complementary method for analyzing the best oncological care, although less powerful than a clinical trial, calls for the development of large clinical and biological databases. The cooperation of neurosurgeons, neurologists, oncologists, radiotherapists, pathologists, biologists, etc., with epidemiologists would be the preliminary phase. 7,8,11,31,85,86 The secondary phase would entail recording clinical and biological prognostic factors, imaging
Assessment at clinical presentation

- Full clinical history and exam, Karnofsky Performance Status (KPS), Mini-Mental State Examination (MMSE), or Montreal Cognitive Assessment (MoCA).
- Initial MRI exam, to perform intracerebral masses characterization, volume evaluation and delineation, includes conventional pre- and postcontrast T1, T2, T2*, and FLAIR sequences as well as diffusion-weighted MR imaging, perfusion-weighted MR imaging and 1H spectroscopy.
- Complementary exams if necessary, including chest CT, abdominal and pelvic CT, and PET-CT, etc.

Multidisciplinary discussion and questions needing answers before making a therapeutic decision

Because there is no standard of care for elderly GBM patients, we suggest a systematic discussion of each individual case in multidisciplinary meetings (with neurosurgeon, medical oncologist, radiation oncologist, neurologist, neuroradiologist, neuropathologist, geriatric physician, etc.) together with the patient (and/or the family) themselves, in order to answer the following suggested questions:
- Does multimodal MRI suggest high-grade glioma?
- Do steroids improve the symptoms?
- Based on the topography of the lesion and limited infiltration, is total or subtotal resection (or partial in case of mass effect) adapted?
- Does the patient’s general condition allow for surgery (resection/biopsy) and for radiotherapy and/or chemotherapy?
- Does the residual (postsurgical) tumor volume allow for radiotherapy?

The first goal of any oncological treatment in elderly GBM patients is to maintain QoL and independence, so the followed proposed attitude is to adapt therapeutics to each individual case.

Surgical care management: resection, biopsy, or best supportive care?

**Rationale for resection**

1. The general treatment goal is to achieve maximal resection without causing an iatrogenic deficit. A resection is typically stopped when the tumor involves functional areas or deep eloquent structures, as confirmed by anatomical mapping (surgical navigation, ultrasound, anatomical landmark (eg, for surgical loectomy, etc.) and/or intraoperative functional mapping, largely depending upon the surgeon’s preference.
2. Based on the topography, the volume, and the delimitation of the tumor, resection is usually proposed for a presumed extent of at least 70% or residual volume ≤5 cm³. Sometimes, we can consider partial resection when an important mass effect exists with associated clinical signs.

**Assessment of operability**

Assessment of operability includes preanesthetic evaluation (and complementary exams, if necessary), Charlson Comorbidity Index (CCI), poststeroid KPS (KPS6), poststeroid MMSE or MoCA, and comprehensive geriatric assessment (CGA) when 3≤CCI≤8.

Proposed decision tree before surgery

![Decision Tree](image)

**Fig. 1.** Suggested personal, nonstandardized approach for oncology care management of elderly patients (aged ≥70 years) with presumed and confirmed newly diagnosed glioblastoma (GBM). **CGA includes G8 questionnaire, IADL questionnaire, information about social situation, Charlson Comorbidity Index (CCI) (available at http://oncology.oxfordjournals.org/content/suppl/2010/11/08/mdq687.DC1/Appendix_ETCGA_dataset.doc), geriatric consultation, and other exams according to the preference of the geriatric physician (eg, balance and gait assessment, anxiety scale, etc.)**

**When the rationale supports the resection, but the post steroids MMSE or MoCA is very low, the proposal could be directed towards biopsy or best supportive care.** At the presurgical stage, when hesitating between biopsy and best supportive care, if there is no possibility of radiotherapy or chemotherapy, we suggest opting for the best supportive care. **TMZ: temozolomide; Stupp protocol and RT40Gy/15f-TMZ include concomitant and adjuvant TMZ. Note: When high volumes are to be irradiated, we are careful to propose treatments that include radiotherapy, but we may also propose TMZ only, especially for methylated MGMT tumors.**
Oncological management after surgery and confirmed histological diagnosis of GBM
Assessment before radiotherapy and/or chemotherapy includes: CCI, pre-therapeutic KPS (KPSₚ), pre-therapeutic MMSEₚ or MoCA, CGA when 3<CCI<8, volume to consider for radiation therapy, tumor methylguanine methyltransferase promoter (MGMTₚ) status, and complementary exams, if necessary.

Proposed decision tree post surgery

Suggested follow up for elderly GBM patients
1) After the end of each treatment or after three months:
   - Classic oncological evaluation (general and neurological evaluation, steroid therapy dosage, MMSE or MoCA, KPS) and MRI.
   - QoL evaluation (QLQ-C30 and BN-20).
   - If possible: G8 questionnaire, IADL questionnaire, information about social situation.
2) Progression-free survival (PFS) and overall survival (OS).

What do we still have to evaluate in clinical practice for each care protocol proposed?
- Impact of CCI and CGA evaluation before treatment.
- Impact of methylated status of MGMTₚ (and the method used).
- QoL, independence, PFS and OS.

Last point: promoting inclusion in clinical trials with biological, QoL, CGA, cognition, independence, PFS and OS evaluations.

Fig. 1. Continued

- Data, successive treatments and responses, OS, QoL, maintenance of functional independence, absence of serious therapy-related side-effects, and burden of treatment.

Health care information systems are expanding rapidly, mainly for economic reasons, and more efficient medical applications will be a major pathway to the future. Computer interface systems have improved dramatically, and advances in health information technology now include mobile devices such as tablet computers and smartphones. A goal for future applications is the direct export of data from medical notes (e.g., operative
reports, pathology reports, QoL evaluations, etc.) and imaging studies into a specific database without having to re-enter anything manually. The difficulties in implementing such a system are not technical but rather involve confidentiality rules and the sharing (or pooling) of medical data between different actors in the healthcare system. First, we can argue that many secure systems are already available, and second that more and more departments are pooling their clinical results. This will be the future.

**Conclusion**

Although there are no standards of care for elderly GBM patients, we can hypothesize that (i) KPS (probably after steroid treatment) is one of the most important clinical factors for determining our oncological strategy; (ii) resection is superior to biopsy, at least in selected patients (depending on the location of the tumor and associated comorbidities); (iii) specific schedules of RT result in modest but significant improvements; (iv) TMZ has acceptable tolerance by elderly GBM patients, even when KPS<70%, and could be proposed after surgery for methylated elderly GBM patients; and (v) the addition of concomitant TMZ to RT has not yet been validated but shows promising results in some studies; however, the optimal schedule of RT remains to be determined.

In the future, in addition to traditional clinical factors (KPS, MMSE, neurological status, etc.), CGA, imaging, and biology will help clinicians propose the best oncological strategy to their patients. Besides clinical trials, database and population studies will also be very important and complementary sources for evaluating classic oncological results (OS and PFS) in "real life" along with QoL, maintenance of functional independence, absence of serious therapy-related side-effects, and treatment burden.

To conclude this work, we suggest a personal, nonprotocol approach for the oncological care and management of elderly patients (aged >70 years) with presumed or confirmed newly diagnosed GBM (Figure 1).

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**References**


