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General review

Management of glioblastomas in the elderly population

F. Laigle-Donadey [a,*], S. Greffard [b]

[a] Service de neurologie Mazarin, hôpital de la Pitié-Salpêtrière, AP–HP, 75651 Paris cedex 13, France
[b] Service de gériatrie hôpital de la Pitié-Salpêtrière, AP–HP, 75651 Paris cedex 13, France

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ABSTRACT

Glioblastoma multiforme (GBM) is the most common primary brain tumor in adults. The incidence of malignant gliomas is growing in the elderly population. Unfortunately, increasing age is one of the most important negative prognostic factors for this tumor. For a long time, the treatment of elderly patients with GBM was controversial. Currently, more active strategies are the rule. Indeed, as in the younger population, prospective randomized studies have recently established the benefit of radiotherapy associated with concomitant and adjuvant chemotherapy by temozolomide in older patients suffering from malignant gliomas with good functional status. The application of chemotherapy alone may be especially useful in patients with poor functional status and O-6-methylguanine-DNA methyltransferase (MGMT) promotor methylation. For the portion of the elderly population identified as frail, treatment decisions should be made in the context of a comprehensive geriatric evaluation while also taking into account quality of life and concomitant pathologies. The willingness of the patient and his or her caregivers will also be key to the therapeutic decision. Symptomatic treatments such as corticosteroids and antiepileptic drugs may be less tolerated in this population compared to younger patients and should be used only if requested. In the future, it will be necessary to continue to develop specific schedules of treatment in the frail population. For this reason, prospective randomized clinical trials are still needed to pursue improvements in the pattern of care of malignant glioma in elderly individuals.

The incidence of cancer, particularly primary brain tumors (BT), in the elderly population is increasing [1,2]. Currently, elderly patients constitute up to 25% of patients presenting with glioblastoma multiforme (GBM), and their number is expected to double in the next 2 decades [3]. However, their optimal management has received little attention for a long time, mainly because of a very poor expected survival (4–6 months). Indeed, older patients have been traditionally excluded from large controlled studies, and in the absence of a standard of care, the management of malignant gliomas in this population was left to the discretion of the responsible physician. Many patients have not been treated vigorously or treated at all [4,5] because of the fear of treatment-related constraints and toxicity.

However, for a few years, some encouraging advances in the pattern of care of younger patients have incited clinicians

* *Corresponding author.*
E-mail addresses: florence.laigle-donadey@aphp.fr (F. Laigle-Donadey), sandrine.greffard@aphp.fr (S. Greffard).
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to test a more vigorous approach in the elderly population as well. Indeed, clinicians have realized that it is no longer possible to manage a growing part of their patient population without relying on ''evidence-based medicine'' data.

Treatment decisions should thus be made optimally in the context of a comprehensive geriatric assessment (CGA). Knowledge of the specificities of elderly patients is a prerequisite for their management. The collaboration between neurologists and geriatricians is essential. This double evaluation is the best guarantee to prevent elderly patients, especially the frailest, from being insufficiently or, conversely, overly treated. In this age group, the main goal is both controlling the tumor and preserving the independence and quality of life of the patients.

1. The notion of ''elderly'' and aging

The term ''elderly patients'' is vague and encompasses heterogeneous patients with a wide range of ages and diverse physiological statuses, and comorbidities [6,7]. The World Health Organization (WHO) sets the age range at $\geq$ 65 years. However, in our aging, Western societies, a patient aged 60–65 years is now considered ''rather young'', deserving aggressive treatment. This trend is also observed in the glioma literature, where the term ''elderly'' currently refers to patients older than 70 or even 75 years (''older old'').

Physiological age, which takes into account organ functions and associated comorbidities, could be a better predictor of patient health status than chronological age itself. Indeed, elderly patients are not equal; for example, some are frail, and others are not.

Aging is classically separated into 3 categories. The first category represents harmonious aging (physiological age below marital status) with the concept of ''successful aging'' [8,9] and is called ''Balducci 1'' or ''fit elderly''. This category includes self-sustaining patients without comorbidities; the proposed treatment for this group is identical to that of a younger one. The second category, called ''Balducci 2'' or ''frail elderly'', applies to patients with 1 or 2 comorbidities and/or functional dependence in performing 1 or 2 activities of daily living (ADL). In these vulnerable patients, treatment must be adapted. The third group, named ''Balducci 3'' or ''unfit elderly'', includes patients with pathological aging who suffer from 3 comorbidities (or more), are functionally dependent in performing ADLs or present with a progressive geriatric syndrome. Tumor prognosis and life expectancy differ depending on the group [10].

2. Identification of frailty: the key role of geriatric assessment

Frailty is a clinical syndrome modulated by comorbidities and psychological, social, economic and behavioral factors. It reflects a decrease in physiological reserve capacities that alter the mechanisms of adaptation to stress [11,12]. Frailty syndrome is a risk factor for higher and pejorative events, such as disability, falls, hospitalization and institutionalization. Age is a major determinant of frailty but does not explain this syndrome alone. Managing the determinants of frailty can reduce or delay its consequences. Thus, frailty would be part of a potentially reversible process.

Several definitions are available for evaluating the risk profile of frail elderly individuals, but a gold standard is unfortunately currently missing.

2.1. *The concept of Comprehensive Geriatric Assessment (CGA)*

Identification of a frail patient should lead to a CGA to provide personalized care; conversely, this evaluation is of little interest for patients presenting harmonious aging (''Balducci 1''), who would be able to undergo classic oncological care.

CGA should then be systematically proposed to all patients from 70–75 years of age, who do not have harmonious aging. Once frailty is detected, geriatricians must, if possible, treat it or prevent its aggravation. CGA allows the division of elderly individuals into the three groups of aging, providing information on the patient's comorbidities, physiological age, cognitive and functional status, psychosocial and environmental aspects, and then the overall health level as well as the patient's life expectancy. CGA involves a battery of validated tests: ADL; Instrumental Activity of Daily Living (IADL); mini nutritional assessment (MNA); Mini-Mental State Evaluation (MMSE); Geriatric Depression Scale (GDS); and Cumulative Illness Rating Scale for Geriatrics (CIRSG).

However, overall, it is estimated that CGA influences the therapeutic decision in 20% of patients.

Indeed, CGA has limitations and weaknesses. Because it is time consuming, it is not routinely performed by specialists other than geriatricians in addition to their usual evaluation. Moreover, this assessment is not standardized, and comparison of CGAs from one study to another is difficult.

Overall, in geriatrics, CGA has demonstrated that it can improve patient quality of life and promote maintenance at home while reducing the rate of hospitalization [13]. In oncology, its impact is less clear, but it is recommended by national and international societies [14]. An Italian team recently published retrospective data regarding the validation of CGA as a predictor of mortality in glioblastoma. Among 113 patients aged 65 years or older, evaluated by CGA, they found a median overall survival of 16.5, 12.1, and 10.3 months in fit, vulnerable, and frail patients respectively ($P = 0.1$). On multivariate analysis, the CGA score appeared to be an independent predictor of survival; indeed, vulnerable and frail patients had a hazard ratio of 1.5 and 2.2, respectively, compared to fit patients ($P = 0.04$). No association between CGA and progression-free survival (PFS) was demonstrated. These promising results suggest that CGA could be a useful treatment decision tool, but validation in largest prospective studies is still needed [15].

By grouping the information gathered during CGA, physicians can determine the type of aging and thus adapt the therapeutic program appropriately [9]. It is important to remember that CGA can be repeated in the same patient whenever a therapeutic decision is needed in order to update the information and suitably adapt the treatment to the patient's physiology. For the moment, this adaptation remains largely empirical. Dedicated studies are required to further develop this approach in the elderly population in the future.

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Table 1 – G8 screening test [16]. G8 screening questionnaire (total score: 0–17). Comprehensive geriatric assessment is needed if the score ≤ 14.

Category	Score (range 0–17)
Age (years)	
< 80	0
80–85	1
> 85	2
Decline of food intake over the past 3 months	
Severe decrease in food intake	0
Moderate decrease in food intake	1
No decrease in food intake	2
Weight loss during the last 3 months	
Weight loss > 3 kg	0
Unknown	1
Weight loss between 1 and 3 kg	2
No weight loss	3
Mobility	
Bed or chair bound	0
Able to get out of bed/chair but does not go out	1
Goes out	2
Neuropsychological problems	
Severe dementia or depression	0
Mild dementia or depression	1
No psychological problems	2
Body mass index (BMI)	
BMI < 19	0
BMI 19–21	1
BMI 21–23	2
BMI ≥ 23	3
Takes more than 3 medications per day	
Yes	0
No	1
Self-rated health (in comparison with people of the same age)	
Not as good	0
Unknown	0.5
As good	1
Better	2

2.2. *Interest of the G8 scale*

Unfortunately, obtaining a detailed evaluation by a geriatrician for each elderly patient may not be reasonable in daily practice. However, in patients with a harmonious aging (generally 20 to 30% of the population), it is conceivable that this evaluation could be performed by an oncologist or a neurologist who is used to treating elderly patients; the use of the Oncodage or the G8 test then avoids unnecessary evaluations and allows focus on the most frail patients [16].

G8 or Oncodage (Table 1) is an interesting screening test of frailty initiated by a French group [17]. This tool includes 8 items for studying the nutritional and physical status of elderly patients. It can be performed by a nonspecialist in less than 5 min. It is probably the best screening test for fragility [18], even its lack of specificity. A score ≤ 14 requires a geriatric evaluation; a higher score allows for an oncological treatment without a particular risk. Recently, a French monocentric retrospective study demonstrated the interest of this screening scale, specifically in the management of glioblastomas, showing on multivariate analysis that the G8 score was a significant, independent predictive factor of overall survival [19]. We think that the G8 could be systematically associated with the main screening tools classically used by neurooncologists as a criterion of ''independence'', such as the Karnofsky Performance Status (KPS) or the ECOG Performance Score (Table 2) because of the great imperfections of both.

3. Increasing incidence of primary brain tumors in elderly patients

Several recent studies confirm the increasing incidence of brain tumors in older patients, with an estimated annual incidence of 6000 elderly patients in the U.S.

The number of elderly GBM patients is expected to double in the next 2 decades [3]. A more generalized use of

Table 2 – ECOG performance status and KPS Score.

ECOG performance status	Karnofsky performance status
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited self-care; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any self-care; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

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noninvasive diagnostic technology such as CT or MRI and a more aggressive workup in this age group are possible explanations for this finding [20].

Previous radiotherapy is the only recognized causal factor of sporadic brain tumors, and cases of radiation-induced gliomas occurring several decades after a previous irradiation are increasingly reported in elderly patients.

4. A particularly dismal prognosis at this age of life

It has long been established that increasing age is one of the most pejorative prognostic factors for the survival of patients with malignant gliomas, for a reason still unknown. One of the hypotheses initially discussed in the literature was that the diagnostic and therapeutic management of gliomas in older patients was suboptimal until a few years ago. For example, some studies suggest that elderly patients are less likely to be referred to specialized centers and to receive vigorous therapy, such as surgery [4,5,21]. Even in specialized centers, elderly patients are underrepresented in clinical trials, in part due to the reluctance of clinicians to include them due to a fear of side effects, even if old age is often by itself an exclusion criterion of many trials [6]. The potential danger is that in this group, appropriate treatment is not initiated, and the patient worsens and dies: this circular reasoning is called a self-fulfilling prophecy (Pygmalion's effect). Advancement in age alone should not be an exclusion criterion for the care of elderly patients. As previously detailed, CGA has to play a key role in decision treatment.

Finally, another key explanation is that malignant gliomas may have specific age-related biological characteristics in the elderly. For example, the isocitrate dehydrogenase (IDH) gene mutation, which correlates with a better overall survival (OS) compared to IDH wild-type gliomas, is much more uncommon in elderly GBM patients compared to younger adult GBM patients [22]. Conversely, the incidence of O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, which is known to be associated with greater sensitivity to alkylation, seems to be higher in elderly patients; it was found on the 220 samples of Ferguson et al in 41% of younger patients vs 49% of older patients in histologically-defined GBM. When IDH wild-type GBM samples alone were analyzed, elderly patients showed significantly increased MGMT promoter methylation relative to younger patients (48% [43/89] versus 31% [21/6], respectively; $P = 0.0334$)[23]. *p53* mutations and EGFR amplifications seem to pose opposite prognostic values in a young compared to an elderly GBM patient [24]. This key point is still under investigation [4].

5. Management of gliomas in elderly patients

It is important to emphasize the fact that an active way of acting should be part of a global objective for improving survival but also to preserve quality of life.

First, the main clinical manifestations of brain tumors include intracranial hypertension, epileptic seizures and/or various neurological deficits depending on tumoral location, which may justify some symptomatic treatments.

5.1. *Symptomatic treatment*

5.1.1. *Treatment of epilepsy*

Anti-epileptic drugs have no preventive indication in gliomas. However, if they are necessary, they may cause adverse effects that may be worse in older than in younger patients. The cognitive impairment due to antiepileptic treatment, including frequent psychomotor slow-down, can particularly impact the daily quality of life of elderly patients. Conversely, severe morbidities can result from seizures in this population, such as fractures [25]. Ideally, an anti-epileptic drug used in elderly patients should have a clearance unaffected by renal impairment, no hepatic inducer or inhibitor effect, and no severe side effects, especially neurotoxicity. It is important to favor a monotherapy with a nonsedative molecule and without a notable cognitive effect (i.e., a molecule with ''good cognitive profile''). The dose used is lower than in younger patients. The initiation of treatment is based on the rule ''start low, go slow''. Elderly patients have a high sensitivity to drug side effects, some of which are dose dependent. It is also important to simplify the prescription as much as possible to improve compliance and avoid errors. The number of doses will be limited by using a galenic adapted to elderly patients. The ''newer'' anti-epileptic drugs, with no (or almost no) inducer and no inhibitor effects, are promising in the elderly population [26]. In practice, expert consensuses recommend starting treatment in the elderly population with lamotrigine or levetiracetam.

5.1.2. *Corticosteroids*

Prescription patterns in elderly individuals are the same as in the young adult. The surveillance and prevention of the occurrence of side effects of these treatments must be particularly rigorous in the population of people over 75 years.

The tolerance of corticosteroid therapy (used as anti-edematous) is lower in this population. They are not specific to older people but are potentially more debilitating. These side effects, although well known, are often neglected in practice.

The risk of side effects mainly depends on the dose and duration of treatment (> 3 months). Short-term corticotherapy is at risk of producing delirium or behavioral changes (depressive), and it can cause hypertension with an increased risk of heart failure. Long-term corticotherapy may be particularly detrimental in elderly individuals, leading to more osseous, cutaneous, and infectious complications as well as proximal muscle loss. It is then mandatory to use the minimal efficient dosage and prescribe preventive measures such as physical therapy as well as usual associated pills (vitamin-calcic supplementation, bisphosphonate...) [27].

5.1.3. *Antibioprophylaxis*

Prevention against pneumocystis is currently used in brain tumor patients in cases of lymphopenia or prolonged high-dose corticotherapy [28]. Some teams also recommend systematic prophylaxis for all elderly patients because of the very common incidence of immunodepression at this age of life. The most widely used antibiotic is sulfamethoxazole.

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5.2. *Antitumor therapy*

Therapeutic management, however, even if it is partially standardized (Fig. 1), should be individualized as much as possible. A table allows an overview of main clinical trials conducted in elderly GBM patients (Table 3). Patient opinion remains a key element to be collected.

5.2.1. *The role of aggressive surgery*

As a rule, histological diagnosis remains necessary to eliminate another diagnosis (particularly a curable disease such as a cerebral abscess) and to analyze tumor histomolecular subtypes. Indeed, to define precisely the tumoral subtype is a key issue. For example, grade II and III astrocytomas presenting with GBM molecular alterations are now considered as "Diffuse astrocytic glioma with GBM molecular features grade IV"; therefore, molecular testing is important also in elderly patients in whom a molecular GBM may be discovered even if histology is that of a lower grade, then avoiding misdiagnoses.

New multimodal MRI techniques (spectroscopy and perfusion), despite being very useful, do not constitute a formal proof of a diagnosis. It is often believed that elderly patients recover more slowly from aggressive therapy, particularly surgery and are at a higher risk for postoperative neurologic deterioration. Nevertheless, thanks to the improvement of surgical and anesthesia techniques, it seems that this risk is much lower than expected and that tumoral debulking in elderly patients is not associated with a higher risk of complications during or after the procedure than in the youngest patients. Retrospective studies seem to show a benefit of resection (gross total and subtotal) to OS when compared to biopsy alone, similar to results described for younger patients, with patients undergoing a gross total resection (GTR) demonstrating the greatest benefit in OS [3,28]. Chaichana reported several negative prognostic factors for elderly GBM patients undergoing GTR, including a preoperative KPS < 80, chronic obstructive pulmonary disease, presentation of motor/language/cognitive deficits and tumor largest diameter > 4 cm [29].

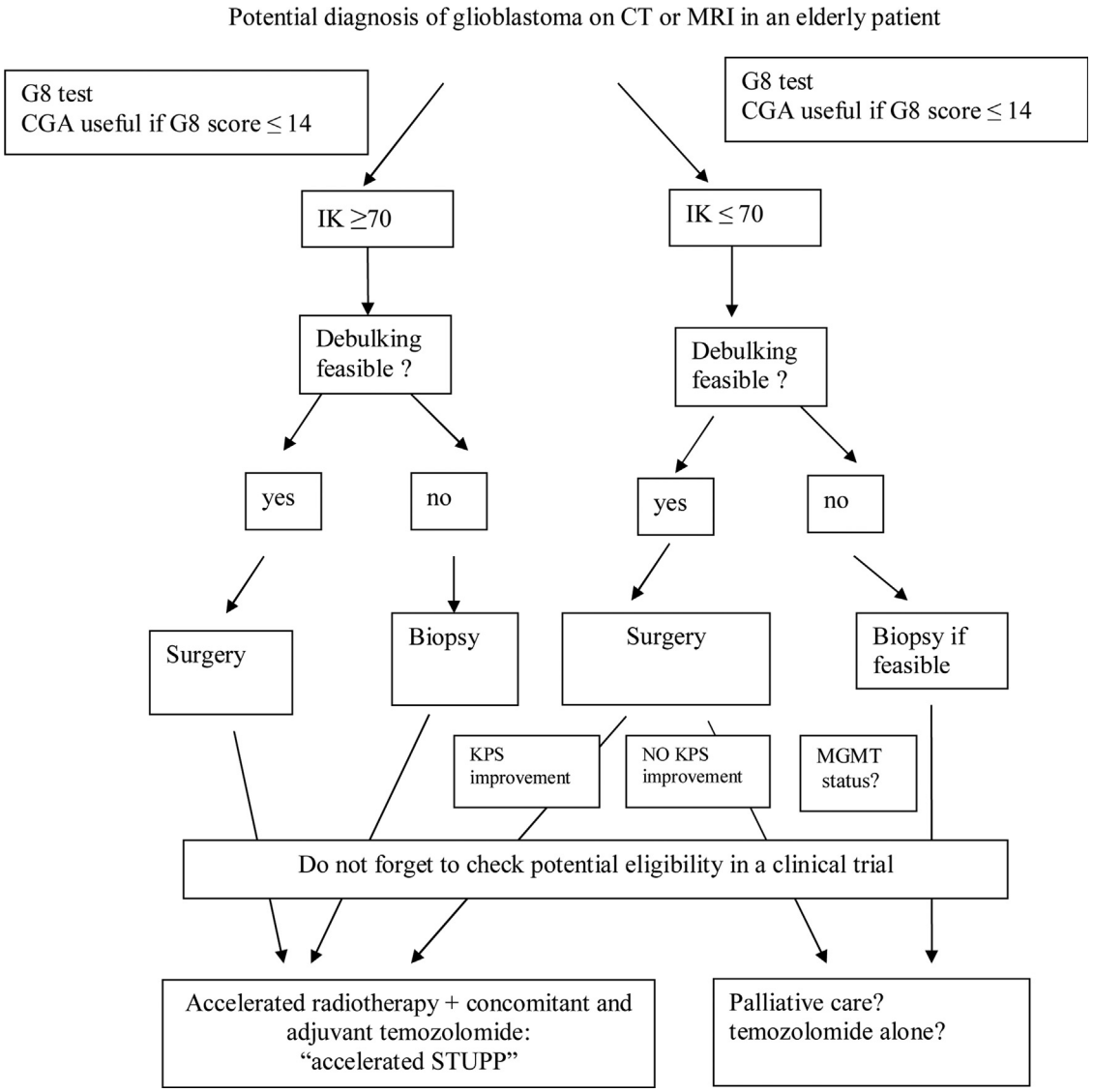

Fig. 1 – Algorithm of pattern of care for elderly glioblastoma.

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Table 3 – Results of main clinical trials conducted in elderly patients with newly diagnosed glioblastoma.

Study, Year	Treatment arms	Number of patients	Median PFS	P-value	Median OS (mth)	P-value	OS at 1 year (%)
Roa, 2004	Normofractionated RT (6 wk)	47	NA	NA	5.1	NA	44.7
	Hypofractionated RT (3 wk)	48	NA		5.6		41.7
Keime-Guibert, 2007	Normofractionated RT (5.5 wk)	39	3.8	$P < 0.001$	6.8	$P = 0.002$	12
	Best supportive care	42	1.3		3.9		0
Gallego, 2011	TMZ alone in poor PS patients[a]	70	4		6.2		
Malmstrom, 2012	TMZ monotherapy	119	NA	NA	8.3	$P = 0.01$	27
	Hypofractionated RT (2wk)	123	NA		7.5	$P = 0.24$	23
	Normofractionated RT (6wk)	100	NA		6		17
Wick, 2012	TMZ monotherapy	195	3.3	$P < 0.001$	8.6	$P < 0.001$	34.4
	Normofractionated RT (6 wk)	178	4.7		9.6		37.4
Perry, 2017	Hypofractionated RT (3 wk)	271	3.9	$P < 0.001$	7.6	$P < 0.001$	22.2
	Hypofractionated RT (3 wk) + TMZ	271	5.3		9.3		37.8
de Castro, 2017	Hypofractionated RT (3 wk)	35	3.2	$P = 0.706$	6.2	$P = 0.936$	10
	Extremely hypofractionated RT (1 wk)	26	4.3		6.8		18
Yusuf, 2018	Hypofractionated RT (2-wk)	10	6		NR		53.3
Wirsching, 2018	Hypofractionated RT (3 wk) + BEV	50	7.6	$P = 0.003$	12.1	$P = 0.77$	54
	Hypofractionated RT (3 wk)	25	4.8		12.2		56
Reyes Botero, 2018	TMZ Plus BEV in poor PS patients[a]	66	3.8		5.9		NA

RT: radiotherapy; BEV: Bevacizumab; TMZ: Temozolomide; wk: week; mth: month; PS: Performance Status; NA: not available; NR: not reached; OS: overall survival; PFS: Progression Free Survival.
[a] Studies specifically dedicated to elderly GBM patients with poor PS.

Regarding prospective data, the value of debulking GBM in elderly patients has been shown in a small Finnish randomized clinical trial reported by Vuorinen et al. [30] a few years ago. In that study, 23 patients aged over 65 years with malignant glioma (83% with GBM) were randomly assigned to biopsy only or to surgical resection, followed by radiotherapy. The median survival time was significantly longer with resection, 5.6 months, compared to 2.8 months with biopsy. When compared to biopsy, resection was also associated with an improved quality of life. This study also showed the high risk of preoperatory diagnosis mistakes (histological diagnosis did not confirm a malignant glioma in up to ¼ of patients). These data are encouraging, but they are preliminary because of the very small number of evaluated patients. A large prospective randomized study evaluating the impact of surgery on malignant gliomas on survival and quality of life in elderly patients in cases of operability and lack of anesthetic contraindication has just been completed at the national level in France to obtain strong justification of such a pattern of care. While waiting for the results of this prospective randomized "CSA" trial, (closed trial, data currently under analysis), a surgical resection is recommended in the meantime after neurological and geriatric evaluation of the risk/benefit balance.

5.2.2. *The role of radiotherapy*

Twenty years ago, the value of radiotherapy (RT) in older patients with glioblastoma was still questioned because of the debated data issued from retrospective studies [31,32]. Due to recent prospective studies, radiotherapy has now found its place in the standard of care of gliomas of elderly patients that have a particular clinical and functional status (IK $\geq$ 70) [33]. It was initially demonstrated by a French prospective phase III study coordinated by ANOCEF (Association des Neuro-OnCologues d'Expression Française), which included 81 patients suffering from newly diagnosed malignant gliomas with a KPS of at least 70. After biopsy or surgery, patients were randomly assigned to receive either supportive care (corticosteroids, anticonvulsants, palliative support) or supportive care and focal radiotherapy (50 Gy/28 fractions/38 days). Patients who received radiotherapy had a better median survival (29.1 weeks) than patients who only had supportive care (16.7 weeks, $P = 0.002$), without further impairment of quality of life or cognitive functions.

Another issue is the schema of radiotherapy to adopt. Indeed, the "classical" intensive course of 60 Gy delivered over 6 weeks is "too" long if one realizes that the duration of treatment might take up to a third of the patient's remaining life [31]. Recently, several studies [34–36] have addressed the issue of hypofractionation for patients with poor prognoses to reduce treatment time, with apparently similar results on survival compared with conventional courses. This issue was specifically examined by Roa et al. [34] in a prospective randomized study of patients aged over 60 years with a similar median survival (5.1 and 5.6 months, respectively) in patients who received either a standard course of RT (60 Gy in 30 fractions over 6 weeks) or a short course RT (40 Gy in 15 fractions over 3 weeks). Hypofractionated radiotherapy does not seem to produce increased toxicity in elderly patients, possibly because most patients do not live long enough to develop long-term complications.

Other protocols have been described: 30 Gy in 10 fractions, 34 Gy in 10 fractions, as well as a protocol of tailor-made, hyperaccelerated radiotherapy (5 $\times$ 5 Gy), which is an option also under study in this population, depending on the situation [36–40].

RT, of course, requires patient cooperation and calm and a lack of severe cognitive impairment, which may interfere with the procedure.

5.2.3. *Chemotherapy*

5.2.3.1. *Chemotherapy concomitant to radiotherapy*. In 2005, an EORTC phase III study in patients with glioblastoma under

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the age of 70 showed that chemotherapy with temozolomide (TMZ) administered during and after radiotherapy increased survival compared with radiotherapy alone, and this protocol, nicknamed the ''STUPP regimen'', is to date the standard of care for ''young'' patients [41]. In elderly patients, after encouraging retrospective results in terms of median survival (11 months) [42,43], a prospective randomized study named the ''EORTC 26062-22061 trial'' [44] allowed a demonstration of a benefit in terms of global survival and progression-free survival of concomitant and adjuvant chemotherapy by temozolomide associated with accelerated radiotherapy. This transposition of the Stupp regimen or ''accelerated STUPP'' to the elderly population is becoming the new standard of care in patients aged over 70 years with KPS $\geq$ 70.

5.2.3.2. *Chemotherapy alone*. Chemotherapy alone is sometimes used in elderly patients because of its ease of use and the usually good tolerance of drugs such as temozolomide. Cases of responses have been published [45,46].

Some retrospective data and 2 randomized trials conducted in Nordic countries (NOA-8 et Nordic trial) suggest that this treatment could be as efficient as and better tolerated than radiotherapy and then can be used as a therapeutic alternative to accelerated radio-chemotherapy in elderly patients with newly diagnosed GBM and good KPS [47,48]. Knowledge of a patient's MGMT promoter methylation status supports the use of TMZ or RT as single agents in some frail patients [48]. Therefore, chemotherapy alone is sometimes used case by case, mostly in patients with MGMT promotor methylation, depending on the context, after collegial discussion. Thus, some authors recommend managing elderly GBM patients according to MGMT status.

Chemotherapy alone also constitutes an interesting alternative strategy in elderly patients with initial poor performance status (IK $<$ 70) and if radiotherapy is not indicated. These patients frequently receive only palliative care, which is an option, but a study conducted by ANOCEF (''phase 2 TAG trial'') showed that a treatment of temozolomide can be beneficial in terms of survival or quality of life even in this group of particularly very bad prognoses. The reported median PFS and OS were 16 weeks and 25 weeks, respectively. Positive MGMT promoter methylation status was noted to be associated with improved PFS and OS (26 vs 11 weeks and 31 vs 19 weeks, respectively) [49]. Another study was also conducted by ANOCEF (''phase 2 ATAG trial'') in view to analyze the benefit of the combination of bevacizumab plus temozolomide in this particularly severe population, not eligible to RT. Results suggest that this treatment is active in elderly patients with GBM and low KPS, with an acceptable tolerance level; however, whether this combination is superior to temozolomide alone remains to be demonstrated by a randomized study [50].

Moreover, the interest of bevacizumab in addition to hypofractionated radiotherapy versus radiotherapy alone was also questioned in a phase 2 trial dedicated to elderly GBM; despite a benefit in terms of median PFS, which was longer in arm bevacizumab + RT than in arm RT alone (7.6 and 4.8 months respectively; $P = 0.003$), this association was disappointing, because it did not prolong survival in elderly glioblastoma patients [51].

The main side effects of temozolomide are fatigue and constipation mainly secondary to vomit prevention by setrons, as well as an increasing risk of infectious complications (pulmonary, intestinal...), which can be particularly severe in this population. These effects must increase the prescriber's vigilance (clinical, biological monitoring...) and trigger symptomatic measures if necessary.

5.3. *Supportive care*

It is important to emphasize that the pattern of care of elderly patients suffering from malignant gliomas must be continuously considered throughout the illness, from diagnosis to the palliative care phase, because of the particularly dismal prognosis at this age of life. Indeed, a vigorous pattern of care, far from ignoring this aspect, is not incompatible with the anticipated, high-quality supportive care. In this context, it will always be necessary to weight the benefit of treatment in terms of quality of life and to prioritize comfort throughout the illness. Associated measures aim to prevent thromboembolic diseases (nursing, heparin), swallowing disorders (speech therapist, adapted food), and so on. A detailed evaluation of the social environment is also a key part of the pattern of care of elderly patients with glioma. It is important to discuss these matters with the patient and his or her caregivers to anticipate the best living place to choose at each step of the disease, depending on the motor and cognitive impairment of the patient and the burden imposed on the caregivers. Comprehensive care, alongside social care (e.g., human assistance), physiotherapy and home improvement by an occupational therapist is then fundamental to keeping the patient at home as long as it is whished. The contribution of coordination nurses is fundamental in this stronger link between hospital and home. Mood disorders should be managed at least by the establishment of psychological support and, if necessary, by the introduction of an antidepressant.

6. Conclusion

The management of elderly patients suffering from GBM has recently evolved due to encouraging results of recent multicentric prospective studies to more vigorous care. Concomitant and adjuvant TMZ and RT are appropriate for patients with good functional status. Frail patients may be considered for less aggressive approaches, such as single-agent TMZ. Many questions remain unsolved. A better comprehension of the specificity of the molecular biology of glioblastomas at this age of life is mandatory to better predict the therapeutic efficacy of a treatment weighed against its potential toxicity. Decisions regarding the pattern of care should be made by a multidisciplinary team, taking into account prognostic factors, such as performance status, cognitive functions, tumor operability, associated comorbidities, choice of patients and families. Therapeutic decisions should therefore be tailored to the individual. The evaluation of frailty and comprehensive geriatric assessments in this population is a key issue. Physician education and better collaboration between neurologists and geriatricians are then necessary to improve patient care.

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Disclosure of interest

The authors have not supplied their declaration of competing interest.

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