Treating glioblastoma patients with poor performance status: where do we go from here?

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Practice Points

- Approximately one third of all glioblastoma (GBM) patients exhibit an impaired functional status in the perioperative setting. These patients are usually excluded from large clinical trials because of their dismal prognosis.
- The characteristics of these patients and the exact reasons why they exhibit an altered performance status (PS) have not been appropriately studied.
- Preoperative and postoperative poor PS should be distinguished for practical purposes, since in the former case it might be ameliorated by tumor resection.
- The only available prospective study in poor PS patients has been performed in elderly patients (≥ 70 years). In this population, treatment with temozolomide was shown to be safe and to be associated with a clinically significant improvement of PS in one third of patients.
- Young patients (< 70 years) with poor PS can benefit from temozolomide radiochemotherapy, abbreviated radiation courses, upfront chemotherapy or early use of bevacizumab.
- Prospective studies dedicated to GBM patients with poor PS are needed.

SUMMARY Approximately one third of all glioblastoma patients exhibit an impaired functional status in the perioperative setting. Their optimal management is difficult to define. The only available prospective study in poor performance status (PS) patients has been performed in elderly patients (≥ 70 years). In this population, treatment with temozolomide was shown to be safe and to be associated with a clinically significant improvement of PS in one third of patients. In young patients (< 70 years), daily clinical experience and retrospective data show that some patients can benefit from temozolomide radiochemotherapy, abbreviated radiation courses, upfront chemotherapy or early use of bevacizumab. However, prospective studies are needed to correctly evaluate these strategies, namely their impact on functional status and quality of life.

Glioblastoma (GBM) is the most frequent malignant primary brain tumor in adults [1]. Despite recent advances in treatment, the prognosis of patients with this disease remains dismal. This is especially true in those patients with impaired functional status (Karnofsky performance score [KPS] ≤ 60 [Table 1](#)), a major pejorative independent prognostic factor in this disease. Within the last decade, important advances have been made regarding the management of young patients (< 70 years) with good performance status (PS) [2]. The management of elderly patients (≥ 70 years) has also improved thanks to several Phase III trials demonstrating that patients with good PS benefit from radiotherapy or chemotherapy with temozolomide [3–5]. The management of GBM patients with poor PS, whether in young or elderly individuals, remains very difficult because of the lack

KEYWORDS

• glioblastoma • Karnofsky performance score • poor performance status

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Table 1. Conversion from Eastern Cooperative Oncology Group performance status to Karfnofsky performance score.

ECOG PS	KPS	
0 Asymptomatic	100	Normal; no complaints; no evidence of disease
1 Symptomatic but completely ambulatory	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
2 Symptomatic, <50% in bed during the day	70	Cares for self; unable to carry on normal activity or to do active work
	60	Requires occasional assistance, but is able to care for most of his personal needs
3 Symptomatic, >50% in bed, but not bedbound	50	Requires considerable assistance and frequent medical care
	40	Disabled; requires special care and assistance
4 Bedbound	30	Severely disabled; hospital admission is indicated although death not imminent
	20	Very sick; hospital admission necessary; active supportive treatment necessary
	10	Moribund; fatal processes progressing rapidly
5 Dead	0	Dead

ECOG: Eastern Cooperative Oncology Group; KPS: Karfnofsky Performance Score; PS: Performance status.
Data taken from [6].

of prospective studies dedicated to this fragile population. The purpose of this article is to provide a concise review of epidemiological, prognostic and therapeutic aspects concerning GBM patients with impaired functional status.

Epidemiology of glioblastoma patients with poor performance status

To the best of our knowledge, no epidemiological study has specifically focused on the rate of GBM patients with poor PS and the specific characteristics of these patients, including the reasons why they have a poor PS. In addition, the definition of poor PS is not exactly the same based on the rating scale that is used, since Eastern Cooperative Oncology Group (ECOG) PS 2 corresponds to both KPS 60 and to KPS 70 (Table 1) [6].

According to population-based and large monocentric studies, between 18 and 37% of all GBM patients have a poor preoperative PS and 29–37% have a poor postoperative PS (Table 2) [7–17]. In addition, two studies suggested that the rate of patients with a poor postoperative functional status is higher among elderly (46–56%) than among younger patients (19–30%) [7,17].

This distinction between preoperative and postoperative PS is important as some patients with a poor preoperative PS will improve after surgery, while other patients with a good

preoperative PS will become functionally impaired because of perioperative complications and surgically acquired neurologic deficits. In a large prospective study, 34.5% of patients presented perioperative complications and 9.9% of patients presented new neurologic deficits [9]. In two large retrospective studies the rate of patients with a KPS ≤ 70 was similar before and after surgery [10,15]. On the contrary, a recent study on 144 consecutively operated GBM patients reported a decrease in KPS in 39% of the patients after 6 weeks [16]. Therefore, the rates of patients with impaired functional status who will gain a good PS after surgery and the rate of patients with a good KPS who will become functionally altered after surgery remain to be determined.

Similarly, among those patients with a poor postoperative PS, it would be important to know the rate of patients in whom PS is impaired due to the tumor itself, as well as the rate of patients in whom poor PS is a consequence of surgical complications. Indeed, the optimal treatment of these patients is likely to be different. In a recent Spanish population-based study, 22.3% of patients did not receive complementary anti-tumor treatment after surgery because of low postoperative KPS [17]. In these patients, low postoperative KPS was attributed to the tumor in 49% of cases and appeared related to surgical complications in 41% of patients.

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In GBM patients with tumor-related poor PS, the factors responsible for the impairment of functional status remain largely unknown. Whether these tumors harbour distinct molecular characteristics responsible for increased aggressivity remains to be determined. Tumor volume and location within the central nervous system are likely to play a role, as does the delay in diagnosis from first symptoms. Interestingly, as suggested by a retrospective analysis, this last factor might explain why unmarried patients seem to have lower PS at diagnosis than married ones [18].

Prognosis of glioblastoma patients with poor performance status

Preoperative PS has long been recognized as a major independent prognostic factor in GBM patients [1]. This prognostic value of functional status has been mostly studied in patients included in clinical trials, that is, patients mostly exhibiting good PS precisely because

of the selection criteria commonly used in clinical trials. The recently updated Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) for GBM identified PS as the second most important variable [19]. This analysis was performed in a series of 1672 GBM patients that participated in various RTOG trials, 16% of them having a KPS <70. Patients under 50 years of age were split only by KPS, with a median survival of 17.1 months for those with KPS ≥90 and 11.2 months for those with KPS <90. Patients aged 50 years or older were split by KPS ≥70 (median survival, 11.2 months) versus KPS <70 (median survival, 7.3 months). A similar RPA analysis performed in 3 population-based studies of elderly patients found that in such population, PS was the second most important variable in patients who did not undergo surgical resection [12]. Patients who underwent biopsy only were split by KPS ≥70 (median survival, 4.6 months) versus KPS <70 (median survival, 2.3 months).

Table 2. Rate and median survival of patients with poor performance status in recent population-based studies.

Study	N	Median age (years)	Year of diagnosis	Criteria for poor PS	Patients with poor PS (%)	Median survival [†]	Ref.
Badaoui <i>et al.</i>							[7]
All patients	216	66.4	2004 and 2008	Postoperative	29	3.7	
<70 years	134	60.3		KPS ≤60	19	4.3	
>70 years	82	74.5			46	3.5	
Graus <i>et al.</i>							[17]
All patients	834		2008–2010	Postoperative	36	NA	
<70 years	642	59		KPS ≤60 [‡]	30		
>70 years	192	75			56		
Bauchet <i>et al.</i>	474	64	2004	Preoperative	22	6.3	[8]
				KPS ≤60			
Chang <i>et al.</i>	413	58	1997–2000	Preoperative	18	NA	[9]
				KPS ≤60			
Stark <i>et al.</i>	492	62	1990–2007	Preoperative	37	NA	[10]
				KPS ≤60			
				Postoperative	37	NA	
				KPS ≤60			
Zouaoui <i>et al.</i>	149	74.5	2004	Preoperative	27.5	3.4	[11]
>70 years-old				KPS ≤60			
Scott <i>et al.</i>							[12]
>70 years-old	437	75	1979–2007	Preoperative	31	2.3 [§]	
				KPS ≤60			
McNamara <i>et al.</i>	884	62	2004–2010	Preoperative			[13]
				ECOG = 2–3	28	3.7	
				ECOG = 4	5	1.6	
Lutterbach <i>et al.</i>	415	59	1980–2000	Preoperative	32.5	6.7	[14]
				KPS ≤60			

[†]Median survival in months.

[‡]Half of the patients had a KPS = 60 and half of the patients a KPS <60.

[§]Median survival of the patients with KPS <70 who underwent only a biopsy.

ECOG: Eastern Cooperative Oncology Group performance status; KPS: Karnofsky performance status; N: Number of patients in the study; PS: Performance status.

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In population-based studies, PS has also been found to be a strong independent prognostic factor (Table 2). In these studies, the median overall survival (OS) of patients with poor functional status ranged from 1.6 to 6.7 months, being lower in elderly patients (2–3 months) than in their younger counterparts (4–7 months). Some retrospective studies have suggested that the dismal prognosis of GBM patients with poor PS might be partly explained by the fact that such patients less frequently receive antitumor therapies following surgery [20]. Whether this observation is true or not is impossible to assess based on retrospective studies because of evident bias. However, what seems clear is that an important proportion of patients with poor PS do not receive active antitumor treatment after surgery. In a retrospective study dedicated to patients with KPS <60 this was the case for a little more than one third of patients [20,21]. In the previously mentioned Spanish population-based study, 22% of patients were not treated after surgery mostly because of a poor PS. As in this study 36% of patients had a poor KPS, we can suppose that less than half of patients with poor functional status received antitumor treatment after surgery [17]. Assuming that in the recent French population-based study a low PS was also the main reason for not treating patients after surgery yields a similar result: in this population 12% of patients did not receive an oncological treatment and 22% of the patients had a poor PS [8]. In 2008, in our institution, 20% of young GBM patients with poor PS received standard radiochemotherapy

with temozolomide, 44% received chemotherapy or radiotherapy alone, and 36% received only supportive care without specific antitumor therapy [7].

How to treat young glioblastoma patients with poor performance status?

The optimal management of young patients (<70 years) with poor PS is difficult to define because there are no prospective studies dedicated to this population and only few retrospective studies and subgroup analysis of prospective studies are available (Table 3).

In young patients with good PS maximal safe resection of the tumor is recommended [1]. Several retrospective studies have shown that it improves survival, and a prospective study demonstrated that after surgical resection 53% of patients improved clinically [9]. Whether patients with pre-operative poor PS should also undergo maximal safe resection is unknown. Daily clinical experience demonstrates that some patients with pre-operative poor PS can be greatly improved after surgical resection. However, the rates of patients who will be improved and the characteristics of the patients with poor PS who will benefit from surgical resection remain unknown. A retrospective study on the outcome of 100 glioblastoma patients with poor PS who underwent surgical resection suggested that in this population maximal safe surgical resection improved survival [21]. Unfortunately the impact on the PS was not reported. Nevertheless, with age <65 years, tumor size >2 cm and use of temozolomide, radical tumor resection in this series was independently

Table 3. Studies dedicated to poor performance status patients or prospective studies in which information about poor performance status patients is reported.

N	Median age (years)	Treatment	Criteria for poor PS	Patients with poor PS (%)	Median survival [†]	Ref.
70	77	Biopsy and TMZ alone	Postoperative KPS ≤60	100	6.2	[22]
100	54	Surgery +/- RT +/- CT	Preoperative KPS ≤60	100	6.6	[20]
74	69	Biopsy or Surgery +/-RT +/- CT	Postoperative KPS ≤50	100	2.3	[20]
573	56	RT vs RTCT	Postoperative ECOG PS = 2	16	10	[2]
1672	57	RT+CT	Preoperative KPS ≤60	16	6.7–7.5 [‡]	[18]
187	55	TMZ + RT	Postoperative ECOG PS = 2	23	5	[23]
			ECOG PS = 3	7	2	

[†]Median survival in months.
[‡]Patients from the Radiation Therapy Oncology Group database who received radiotherapy and carmustine within RTOG clinical trials. CT: Chemotherapy; ECOG: Eastern Cooperative Oncology Group; KPS: Karnofsky performance score; PS: Performance status; RT: Radiotherapy; RTCT: Temozolomide radiochemotherapy; TMZ: Temozolomide; Corresponds to the median survival of recursive partitioning analysis class V patients.

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associated with better survival. In addition, pre-operative KPS was not associated with survival suggesting that even patients with very low scores (KPS <40) might benefit from surgical resection. Another recent study also suggested that maximal surgical resection might improve the survival of patients with poor PS though to a lower extent than in patients with good PS [24]. On the other hand, several studies have demonstrated that patients with good PS who develop new neurological deficits and/or become non-ambulatory after surgery are less likely to receive an oncological treatment and have a poor prognosis [16,25]. Therefore, it seems that patients with poor PS should undergo maximal safe resection when possible, while in patients with good PS maximal resection should be performed as carefully as possible in order to avoid postoperative deterioration of the PS. Patients with impaired postoperative functional status might benefit from rehabilitation. A recent study demonstrated that patients who undergo inpatient rehabilitation have significant functional improvement, and suggested that a structured inpatient rehabilitation program may level the survival field in lower-functioning patients [26].

In young patients with good postoperative PS, the standard postsurgical treatment is radiotherapy with concomitant and adjuvant temozolomide [2]. Whether patients with poor postoperative PS also benefit from this treatment remains unknown. In the EORTC–NCIC Phase III trial only 16% of patients had a poor PS (ECOG = 2). In a subgroup analysis, there was no benefit of temozolomide chemoradiotherapy in this population. Median survival was 10.5 months in patients treated with radiotherapy alone versus 9.9 months in patients treated with temozolomide radiochemotherapy [2]. In a subsequent analysis, it was shown that patients with the poorest prognosis included in the EORTC–NCIC phase III (i.e., RPA class V patients) also benefited from temozolomide radiochemotherapy [27]. Though RPA class V includes both patients aged ≥ 50 years with good PS who undergo only a biopsy and patients aged ≥ 50 years with poor PS, it is generally accepted to offer young patients with poor PS the multimodal treatment in an attempt to precisely obtain a symptomatic and functional improvement. Two recent retrospective studies dedicated to poor PS patients suggest that these patients benefit from temozolomide radiochemotherapy [20,21]. In one of these studies on 74 patients with

a KPS ≤ 50 , patients treated with temozolomide radiochemotherapy had a better outcome than those treated with radiotherapy alone (9.8 vs 1.6 months) and those treated with radiotherapy, with or without temozolomide, had better outcome than those who declined radiotherapy (5.2 vs 1.6 months) [20]. Interestingly, in this study approximately 50% of patients who survived more than 3 months following radiotherapy had an improvement of 20–30 points in the KPS score. Nevertheless, an important concern in patients with poor PS remains the tolerance of radiotherapy. In elderly patients, abbreviated radiotherapy regimens have been shown to be at least equally effective and better tolerated than the classic regimen [4,28]. Several single-institution studies have tested abbreviated regimens in patients with poor PS using radiotherapy alone or in combination with temozolomide [29–31]. These studies however most often included both young patients with poor PS and elderly patients with good or poor PS and are therefore difficult to analyze. In a study that included 54% of patients with poor PS, an improvement of KPS was observed in approximately 50% of patients after treatment using an abbreviated course of radiotherapy consisting of 40 Gy in 15 fractions with concurrent temozolomide [30]. Certain other studies have analyzed over the past two decades the role of hypofractionated radiotherapy in patients with newly diagnosed GBM, including both patients with good and impaired functional status. Nevertheless, such studies are retrospective or small single-arm prospective series that preclude obtaining valid conclusions. Moreover, interpretation of their data is importantly confounded by high heterogeneity in patients' characteristics and in the schedules and doses of radiotherapy [32].

Upfront chemotherapy has also been tested to facilitate radiotherapy, especially in patients with large unresectable tumors. Several studies, most of them performed however in patients with good PS, have reported a 20–50% response rate using various alkylating-based chemotherapy regimens, including temozolomide [23]. In one of these studies, which included 30% of patients with poor PS (KPS = 60), patients with unresectable tumors were treated with up to six cycles of temozolomide and carmustine before receiving radiotherapy [33]. An objective response was noted in 42.5% of patients and median survival of responders was 16 months. Interestingly, in this study, KPS was not found to be a prognostic

factor, suggesting that even patients with poor PS could have a correct outcome if they respond to this chemotherapy regimen. However, in another study in which patients with unresectable tumors received two cycles of temozolomide before radiotherapy, the median survival of patients with ECOG 2 and 3 PS remained very poor (5 months for ECOG PS = 2 patients and 2 months for ECOG PS = 3 patients) [23]. The role of upfront chemotherapy in young patients with poor PS therefore remains to be determined. Yet, the results obtained with bevacizumab in the recurrent setting have renewed the interest in this strategy. In patients with recurrent glioblastoma, the use of bevacizumab is associated with a 30–50% radiological response rate, and radiological response is frequently associated with rapid improvement of the neurological status [34]. In a retrospective study, 29.5% of recurrent glioblastoma patients with low PS obtained a KPS ≥ 70 after treatment with bevacizumab [35]. Therefore early use of bevacizumab alone, in association with chemotherapy or with temozolomide chemoradiotherapy, might be an interesting option in patients with poor PS. The response rate to upfront bevacizumab is less well established than the response rate at recurrence. Two studies using bevacizumab in association with temozolomide or irinotecan reported a 20–30% objective response rate, which actually is similar to the response rate reported with temozolomide alone [36,37]. However, the interest of bevacizumab in this setting might be its rapid effect. In a case series of eight patients with poor PS, upfront bevacizumab and temozolomide or fotemustine resulted in clinical improvement in all patients though only two patients had an objective response, the six other patients having a stable disease [38]. The use of bevacizumab might also improve the tolerance of radiotherapy in patients with poor PS. The results of two Phase III trials have shown that the addition of bevacizumab to temozolomide chemoradiotherapy was safe and associated with improved progression-free survival [39,40]. Whether poor PS patients might benefit from this regimen remains to be determined, however in our experience adding bevacizumab to temozolomide radiochemotherapy seems to be a promising strategy to treat poor PS patients.

An algorithm for the management of young GBM patients with poor postoperative PS in whom active treatment is considered is proposed on [Figure 1](#). In patients with tumor-related poor

PS in whom temozolomide radiochemotherapy is thought to be feasible we would recommend to perform this treatment in association with bevacizumab. In patients in whom temozolomide radiochemotherapy is not considered to be feasible (because of tumor volume or patient's too poor neurological condition) we would recommend to start with up-front chemotherapy +/- bevacizumab and to secondly perform temozolomide radiochemotherapy if the patient's neurological condition improves.

How to treat elderly glioblastoma patients with poor performance status?

Previous studies have shown that elderly GBM patients with good performance status do benefit from surgical resection [41], radiotherapy [5] and also from chemotherapy with temozolomide [3–4,42]. Additionally, in an attempt to extrapolate the standard of care in younger individuals, the role of combined chemoradiation is currently being investigated in this old population.

The etiologic management of elderly patients with GBM and poor performance status is more controversial and remains unsettled. Precisely because of their advanced age, comorbidities and deteriorated functional status, these fragile patients are less likely to undergo surgical resection and even biopsy [43–45]. Thus, the specific role of the extent of surgery in this severely impaired population is unknown. On the other hand, both standard and even short-course radiation therapy regimens require daily trips to the hospital and result in increased fatigue. For these reasons, this specific therapeutic approach appears too inappropriate for bedridden and dependent elderly GBM patients with very short survival expectancy. Precisely because of its oral administration and favorable toxicity profile, chemotherapy with temozolomide seems to be, in addition to symptomatic treatment, the only conceivable alternative for these severely impaired patients [46,47]. The efficacy and safety of temozolomide alone (150–200 mg/m² for 5 days every 4 weeks) in this fragile and disabled population was specifically investigated in a recent multicenter non-randomized Phase II trial [22]. The study was conducted on 70 newly-diagnosed GBM patients aged 70 years or older with a postoperative KPS equal or inferior to 60%. A radiological response rate of 26.5% was observed, consisting of two complete responses and 16 partial responses. Median OS was 25 weeks, which far exceeded the 12-week median survival assumed for a

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similar patient population treated with the best symptomatic care alone. Importantly, this modest but meaningful improvement in survival was accompanied by a functional gain in one third of the patients, most of them becoming able of self-caring for a median period of 3 months (ranging from 1 to 9 months). In addition, treatment with temozolomide was generally well tolerated, with hematological and non-hematological toxicity rates similar to those observed in patients younger and with better functional status. Concerning molecular markers, methylation of the O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation was observed in 42% of the assessed patients, and was linked to a substantially better outcome (31 *versus* 19 weeks). Despite the limitations of its non-randomized design, the results of this trial suggest that treatment with temozolomide might be, in addition to symptomatic care, a reasonable therapeutic alternative for this fragile population. This chemotherapeutic approach might be applicable regardless of the MGMT promoter methylation status, on the basis of the lack of a standardized and consistent DNA-based method for testing MGMT promoter methylation status and the absence of alternative therapies. In addition, the fact that some patients with unmethylated tumors also respond to alkylating temozolomide favors this approach.

In an attempt to improve the results of the aforementioned study, another non-randomized Phase II trial assessing the efficacy and safety of upfront temozolomide (130–150 mg/m² for 5 days every 4 weeks) plus bevacizumab (10 mg/kg every 2 weeks) in this elderly GBM population with poor performance status was recently conducted [48]. A total of 66 patients aged 70 years or older with a postbiopsy KPS below 70% were included. Median OS and PFS times were 24 and 16 weeks, respectively. 38% of the patients transiently achieved a KPS of at least 70%, that is, they became capable of self-care. Moreover, non-hematological toxicity consisting mainly in bevacizumab specific toxicity such as hypertension, thromboembolic and hemorrhagic events, was reported in one third of the patients, while grade 3 or 4 hematological toxicity occurred in less than 20% of the patients. Globally, these outcome results appear identical to those obtained in the above-mentioned previous trial on temozolomide alone. They confirm that temozolomide-based treatment is helpful and safe in this fragile GBM population, and

Figure 1. Algorithm for the management of glioblastoma patients with poor postoperative performance status.

*RTCT not feasible because of tumor volume or because of patient's too poor performance status.

CT: Chemotherapy; GBM: Glioblastoma; KPS: Karnofsky performance score; RTCT: Temozolomide radiochemotherapy; TMZ: Temozolomide.

suggest that adding the antiangiogenic agent bevacizumab does not confer additional benefit.

In summary, at this stage, we recommend treating with temozolomide alone older GBM patients with poor PS in whom active treatment is considered (Figure 1).

Conclusion

Although no studies have specifically addressed this issue, approximately one third of all GBM patients might exhibit an impaired functional status in the perioperative setting, this figure being higher among elderly patients. Preoperative and postoperative poor functional status should be distinguished for practical purposes, since in the former case it might be ameliorated in some cases by tumor resection. The characteristics of patients and the exact reasons why these patients exhibit an altered functional status remain unknown prompting further specific studies to address this issue. Because of the more dismal outcome of patients with poor KPS, these are usually excluded from large clinical trials. There

Figure 2. Example of responses in glioblastoma patients with poor performance status. (A) Pretreatment MRI in a 35 year-old glioblastoma (GBM) patient who presented with aphasia and severe right upper limb deficit (Karnofsky performance score [KPS] = 60). (B) The patient underwent a biopsy and was treated with temozolomide radiochemotherapy. The clinical status greatly improved, at last news, 4 years after diagnosis the patient is doing well (KPS = 90) with an MRI showing an excellent persistent response. (C) Pretreatment computed tomography in a 54 year-old GBM patient who presented with severe progressive anterograde amnesia and acute headaches (KPS = 50). (D) The patient underwent a biopsy followed by temozolomide radiochemotherapy. Although MRI demonstrated a good response, the patient remained severely disabled because of his amnesic syndrome (KPS = 50). He died 28 months after diagnosis diagnosis. This case illustrates the particularly challenging treatment of GBM at the splenium of the corpus callosum. (E) Pretreatment MRI in a 70 year-old-patient who presented severe aphasia (KPS = 60). (F) Following biopsy the patient received temozolomide radiochemotherapy associated with bevacizumab. It resulted in rapid clinical improvement (KPS = 80), and a good radiological response was observed on the MRI performed 1 month after the end of radiotherapy. 24 months after diagnosis the patient is still alive with a good performance status (PS). (G) Pretreatment MRI in a 71 year-old with KPS = 50 because of severe dysexecutive syndrome. (H) Upfront treatment with temozolomide resulted in a very good response associated with an improvement of the PS (KPS = 80); overall survival was 18 months. (I) Base-line MRI in a 48 year-old patient who progressively presented with severe dysexecutive and amnesic syndrome. After biopsy and ventriculoperitoneal shunt KPS was 50, mini mental state examination (MMSE) was 20/30. The patient was included in a clinical trial and received two cycles of upfront bevacizumab associated with irinotecan. (J) The patient improved rapidly despite an MRI showing only stable disease with a complete resolution of the contrast-enhancement and of the edema but with no tumor size shrinkage. Thereafter the patient received temozolomide radiochemotherapy without bevacizumab (it was stopped because of wound dehiscence of central venous device). (K) Radiological response was observed on MRI performed one month after the end of radiochemotherapy. (L) MRI performed 4 years after initial diagnosis. At last news the patient is doing well (KPS = 80) and MMSE is 30/30.

is a lack of evidence concerning the optimal management of young patients with GBM and poor PS. In this population, the roles of temozolomide radiochemotherapy, abbreviated radiotherapy courses, upfront chemotherapy and early use of bevacizumab need to be determined with a special focus on their impact on functional status and quality of life. Daily clinical experience demonstrates that some patients can benefit from

these strategies (Figure 2). Contrarily, two recent clinical trials have investigated the role of specific therapies such as temozolomide and bevacizumab in elderly patients with KPS under 70%. The results of these prospective studies suggest that some of these patients harboring the two most important pejorative prognostic factors, advanced age and impaired PS, can substantially benefit from active antitumor treatment. Thus they

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Table 4. Suggested designs for future trials in glioblastoma patients with poor performance status.

Population	Design
Age <70, poor PS but RTCT feasible	RTCT vs RTCT plus bevacizumab
Age <70, poor PS but RTCT not feasible	Two cycles of up-front TMZ followed by RTCT vs two cycles of up-front TMZ plus bevacizumab followed by RTCT plus bevacizumab or accelerated course of RTCT vs accelerated course of RTCT plus bevacizumab
Age >70, poor PS	Accelerated course of RTCT vs accelerated course of RTCT plus bevacizumab vs TMZ alone

PS: Performance status; RTCT: Temozolomide radiochemotherapy; TMZ: Temozolomide.

have demonstrated that although GBM patients with poor KPS have a significantly worse life expectancy compared with those with adequate functioning, etiologic treatments should not be systematically withheld from these patients. On the contrary, the optimal etiologic therapeutic approach of these patients should be individually and carefully considered in multidisciplinary neuro-oncology teams, and further studies investigating the optimal management of both young and elderly patients should be pursued.

Future perspective

Within the last decade, important progress has been achieved in the management of both young and elderly patients with good PS. It is now time to launch specific trials in patients with poor PS (Table 4). These studies should include evolution of functional status and quality of life as important secondary endpoints. In young patients with poor PS, in our opinion, there are two main populations of patients: those who have a poor PS but in whom temozolomide radiochemotherapy is still feasible and those in whom temozolomide radiochemotherapy is not feasible because of the tumour volume and/or because of the too poor functional status. In the first

population, we think that an important issue is now to determine whether adding bevacizumab to standard temozolomide radiochemotherapy might improve the functional status and the prognosis of these patients. Unfortunately these patients were not included in the two recent Phase III trials that evaluated the addition of bevacizumab to temozolomide radiochemotherapy. In the second population, the role of up-front chemotherapy should be investigated with a special focus on the rate of patients who become amenable to temozolomide radiochemotherapy using this strategy. In elderly patients with poor PS, whether accelerated temozolomide radiochemotherapy +/- bevacizumab is superior to temozolomide alone should be determined.

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