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CLINICAL STUDY

Role of irradiation for patients over 80 years old with glioblastoma: a retrospective cohort study

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Abstract To assess efficacy and safety of hypofractionated radiation therapy (HRT) in patients over 80 years old with newly diagnosed glioblastoma (GBM). Between June 2009 and September 2015, patients in this population with a recommendation for radiation therapy from a multidisciplinary tumor board, and a Karnofsky performance status (KPS) ≥60 as assessed by a radiation oncologist, who received HRT (40 Gy/15 fractions) ± concomitant and adjuvant temozolomide (TMZ) were retrospectively analyzed. A total of 21 patients fulfilled the criteria for eligibility. Median KPS was 80 (60–90). After a median follow-up of 5.8 months (IQR 3.7–13.1 months), median overall survival (OS) was 7.5 months (95% CI 4.5–19.1) and the 1-year and 2-year OS were 39.5% (95% CI 21.9–71.2%) and 6.6% (95% CI 1.0–43.3%), respectively. Median progression-free survival (PFS) was 5.8 months (95% CI 3.9–7.7 months), 1-year and 2-year PFS were 15.2% (95% CI 4.4–52.4) and 0%, respectively. Overall, 16 (76.2%) patients presented a recurrence. Overall seven patients (33.3%) needed to be hospitalized during treatment. On univariate analysis, hospitalization was the only variable that correlated with less favourable outcome in terms of both OS (12.2 months versus 3.8 months, $p<0.010$) and PFS (5.8 months versus 3.4 months, $p=0.002$). Our study suggests that HRT is feasible with acceptable tolerance among "very elderly" patients affected by GBM. Patients 80 and older should be considered for management based on RT.

Keywords Glioblastoma · Radiation therapy · Temozolomide · Elderly

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Introduction

Glioblastoma (GBM) is the most common primary malignant central nervous system (CNS) tumour accounting for 46.1% of all primary malignant brain lesions [1]. The median age at diagnosis is 64 years old and incidence increases with age, the highest rates being reported in the decade from 75 to 84 years (15.24 per 100,000) [1]. Due to the aging of the population it is expected that the number of older patients affected by GBM will further increase. By 2030, two-thirds of new diagnoses will be in individuals older than 65 years [2].

Relative survival estimates for GBM are quite low; 5.1% of patients survived 5 years after diagnosis [1]. Age is an unfavourable prognostic factor since older pati ents have a shorter median survival than younger patients as confirmed by several population-based studies [3–5]. Quality of resection,

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presence of comorbidities, reduced performance status and major propensity to develop treatment-related toxicities are described as negative survival prognostic factors [6].

Currently the standard treatment in patients younger than 70 years is 6-week radiotherapy (RT) and temozolomide (TMZ) followed by adjuvant TMZ alone; median overall survival (OS) with this approach is 14.6 months [7]. Treatment is more heterogeneous for older patients as they are often considered frail. Studies carried using the Surveillance, Epidemiology and End Results (SEER) database have showed that elderly patients with GBM are less likely to receive aggressive treatments such as surgery and RT and that the treatment strategy used was strictly a function of age at diagnosis [4, 5]. According to these findings, it is possible that the reduced survival observed might at least in part be related to the habitual under-treatment of these patients [2].

Older patients are often excluded from clinical trials and therefore the optimal management in this group is unclear [3, 8]. However, a randomized study by Keime-Guilbert et al. found that RT increases OS compared to best supportive care alone without reducing quality of life in patients 70 years or older [9]. Recently, two phase III trials concluded that TMZ alone is equivalent to hypofractionated RT in terms of OS while another study reported a similar survival in elderly patients treated with either standard RT or hypofractionated RT [10–12]. In addition, an exploratory sub-group analysis of the study by Stupp et al. showed that the benefit from the addition of TMZ to RT tends to diminish as age increases, especially for patients older than 65 years [7, 13]. Based on these findings the NCIC Clinical Trials Group enrolled 560 patients older than 65 years in a randomized phase III trial of short course RT plus TMZ versus short course radiation alone; these results have not yet been published [14]. Hence, there is no clear consensus among the available studies regarding the treatment of elderly patients.

So far, a clear definition of "elderly" does not exist. The age threshold used in the various studies discussed above is wide and ranges from 60 to 88 years [9–12, 15]. On the other hand, the trial by Stupp et al. enrolled patients of 70 years and less so these results may not apply to older patients [7]. Chronological age is often used in clinical trials to define a patient as "elderly" without taking into account KPS, as a comprehensive geriatric scale should [2]. We conducted a retrospective study on patients more than 80 years old treated for GBM in a single institution with a hypofractionated RT regimen.

Materials and methods

Institutional review board approval was obtained for this retrospective study. The eligibility criteria included: age over than 80 years, histologically confirmed GBM, and treatment performed with short-course RT. Before treatment, all patients were discussed and determined to be suitable for the treatment by a multidisciplinary team. Magnetic resonance imaging (MRI) and clinical information were available up until the time of analysis or the patient's death. Each patients' medical records were reviewed for clinical data, treatment modalities and outcomes.

All patients underwent a clinical examination before treatment, consisting of a complete history, physical and neurologic examination, baseline blood counts and contrast-enhanced MRI of the brain, as per Stupp et al.'protocol [7].

Treatment plan

Before simulation all patients were immobilized with a customized thermoplastic mask. A 2.5 mm slice-thickness simulation CT scan in supine position was performed and then was registered with the pre-RT MRI to delineate the target volumes and organs at risk (OARs) including the brainstem, upper spinal cord, eyes, lenses, retinas, optic pathways, internal ears (cochleas), and the pineal gland. The gross tumour volume (GTV) was generated using the T1 weighted MRI with gadolinium contrast. The clinical target volume (CTV) was created by adding 20 mm to the GTV, taking into account the presence of natural barriers to tumor spread such as ventricles, bone structures or the falx. The planning target volume (PTV) was defined by adding a 3 mm isotropic margin to the CTV. Dosimetric studies were performed using the ISOGRAY® treatment planning system (DOSISOFT, Cachan, France). Patients were treated using a six MV linear accelerator with 3–5 isocentric coplanar/non-coplanar beams, one session a day, 5 days a week, to reach a total dose of 40.05 Gy delivered in 15 fractions of 2.67 Gy each. RT started within 6 weeks of surgery.

Chemotherapy (CHT) consisted of TMZ at a daily dose of 75 mg/m², 7 days a week from the first until the last day of RT. Patients started adjuvant TMZ at the initial dose of 150 mg/m² for the first cycle and 200 mg/m² thereafter for 5 days every 28 days up to 10 cycles. Patients were not given concomitant TMZ if they had low blood counts, renal impairment or hepatic dysfunction. CHT was prescribed according to treating physician preference.

Follow up and toxicities

After treatment, follow-up visits with MRI were performed every 1–2 months. Response was assessed according to Response Assessment in Neuro-Oncology (RANO) criteria [16]. Toxicities were assessed at each follow up visit according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE).

Statistical analysis

OS and progression-free survival (PFS) were analysed from diagnosis until the measured event (death for any cause for OS, local and/or distant progression and/or death from any cause for PFS) or the last follow up date if no event occurred. RT in general started within 45–60 days from surgery. Chi square or Mann–Witney *U* tests were used to compare variables. Survival curves were generated using the Kaplan–Meier method. Univariate analysis with log-rank test was performed for prognostic factors such as age, gender, KPS before and after RT, type of surgery, use of concomitant TMZ and hospitalization (before and during radiation therapy) to identify any predictors of OS and PFS. All statistics were performed using IBM SPSS v.22.

Results

Patient characteristics

Between June 2009 and September 2015, a total of 21 patients met inclusion criteria. Patient characteristics are shown in Table 1. There were 7 men (33.3 %) and 14 women (66.6 %). The median age at the time of RT was 82 years (range 80–88 years). Fourteen patients (66.6 %) underwent biopsy only, two patients (9.5 %) a gross total resection and five (23.8 %) a macroscopic partial resection. The median KPS before RT was 80 (range 60–90). Six patients were in class IV and 15 in class V according to the simplified recursive partitioning analysis (RPA) classification for GBM [8]. The median time of RT initiation following surgery was 21.5 days (IQR 16.75–24.5). The median overall treatment time was 21 days (19–29). Ten patients (47.6 %) completed concomitant TMZ as planned. Six additional patients started adjuvant TMZ and completed a median of 4 cycles (range 1–10). One patient received neoadjuvant TMZ (2 cycles) instead of irradiation due to neurological worsening after severe sepsis. He recovered his initial KPS allowing irradiation (34 Gy in ten fractions). Before RT, 17 patients (80.1 %) required corticosteroids at a median daily dose of 32 mg (range 12–64 mg) and 4 patients (26.8 %) did not.

Table 1 Patient characteristics

Characteristics	n	%
Age		
Median (range)	82	(80–88)
Sex		
Male	7	33.3
Female	14	66.7
Surgery		
Total biopsy	7	33.3
Subtotal biopsy	14	66.7
Baseline KPS		
>70	14	66.7
≤70	7	33.3
RPA		
IV	6	28.6
V	15	71.4
TMZ		
Yes	10	47.6
No	11	52.4
Hospitalization		
Yes	7	33.3
No	14	66.7
Corticosteroids		
Yes	17	81.0
No	4	19.0

KPS Karnofsky performance status, *RPA* recursive partitioning analysis classification, *TMZ* temozolomide

Survival analysis

After a median follow-up of 5.8 months (IQR 3.7–13.1 months), the median OS was 7.5 months (95 % CI 4.5–19.1) while 1-year and 2-year OS were, 39.5 % (95 % CI 21.9–71.2 %) and 6.6 % (95 % CI 1.0– 43.3 %) respectively (Fig. 1). At the time of analysis, 17 (80.1 %) patients had died and 4 (19.9 %) were still alive without progressive disease. Causes of death were undetermined for 2 patients and due to tumor progression for 15 patients. The median, 1-year and 2-year PFS were 5.8 months (95 % CI 3.9–7.7 months), 15.2 % (95 % CI 4.4–52.4) and 0 %. Overall, 16 (76.2 %) patients presented a recurrence (Fig. 2). At univariate analysis, only hospitalization was a significant predictor of OS and PFS (Table 2).

Treatment toxicities

RT was well tolerated among most patients. After RT, the median KPS was 70 (range 50–90). Only one patient required discontinuation of irradiation at 12.8 Gy due to progressive disease.

Alopecia was the most common side effect, occurring in 13 patients (61.9 %). Other Grade I treatment-related toxicities were skin rash in four patients (19.0 %) and nausea in two patients (9.5 %).

In three patients a worsening of neurological symptoms occurred during RT (two patients with Grade 1 and one patient with Grade 2 cognitive disturbance).

During RT, corticosteroids were introduced in three patients (14.3 %) and five patients (23.8 %) required an increase in total daily dose compared to the beginning of treatment. Overall, seven patients (33.3 %) were hospitalised

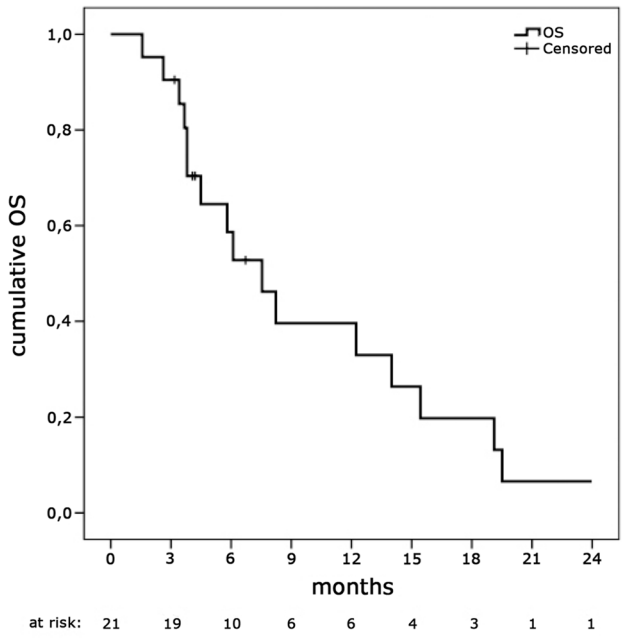

Fig. 1 Kaplan–Meier curve of overall survival (OS) for irradiated patients

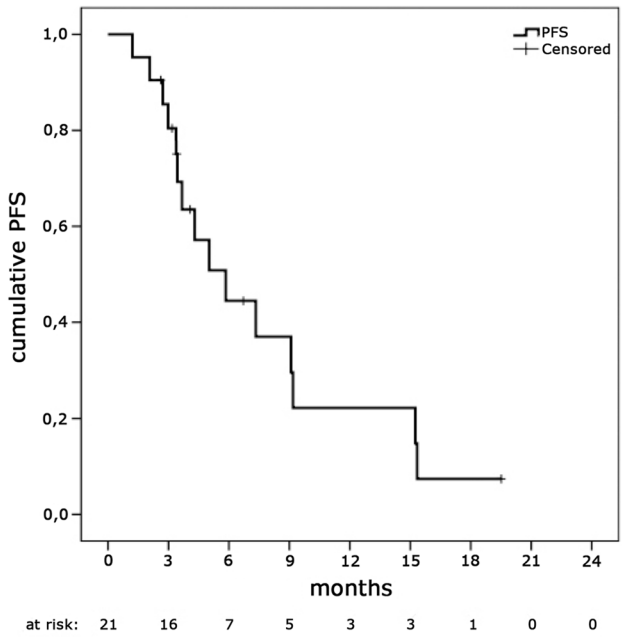

Fig. 2 Kaplan–Meier curve of progression-free survival (PFS) for irradiated patients

due to a decline in overall status: three patients (14.3%) during RT and four (19.0%) before treatment began.

Grade 1 thrombocytopenia occurred in one patient (4.8%) treated with concomitant TMZ. No other haematological toxicities occurred.

In four patients maintenance TMZ was completed while in two patients maintenance CHT was interrupted due to disease progression.

Discussion

To our knowledge, this is the second published series of "very elderly" patients treated with hypofractionated RT. Here RT was delivered in a safe 3-week schedule for patients more than 80 years old (median 82, range 80–91) with a resulting median OS of 7.5 months. In 2008, Idbaih et al. reported favourable results with the same short regimen without CHT (Table 3) [17]. We decided to analyse an older population, so called "very elderly" patients, to fill a gap in the literature caused by inconsistency in the definition of "elderly" (Table 3). Indeed, this definition is currently based on chronological age without taking into account the performance status. Piccirilli et al. treated 22 patients over 80 years old (median age 83.6) with surgery plus RT and/or CHT and reached a median OS of 13.7 months [18]. A recent Japanese multicentre retrospective cohort study analysed the treatment outcomes in 79 patients age 76 and older (median age 78 years) with histologically confirmed GBM [19]. Median PFS and OS were 6.8 and 9.8 months, respectively. The lower OS obtained in our study could be related to the higher number of patients submitted to biopsy as opposite to the studies from Piccirilli et al. and Uzuka et al. In fact, patients that underwent partial/complete surgery had a median OS of 14 months. However, from these data, it appears that RT indication should not be based on chronological age alone. But given the overall paucity of studies for patients 80 years and older, the role of RT remains unclear.

Indeed, because RT may cause neurotoxicity, TMZ, an oral alkylating agent with a low toxicity profile, has been explored in several clinical studies in older patients. Recently, two randomized studies showed that TMZ alone is a valid alternative to RT for elderly patients [11, 12]. Moreover, TMZ should also be considered an acceptable treatment for patients with poor KPS, as demonstrated by a recent phase II trial that evaluated 70 older patients treated with TMZ alone after surgery with encouraging results [20].

In all of these studies, the positive impact of TMZ on survival was related to the MGMT promoter methylation status indicating that patients with methylated tumour may benefit from TMZ. The predictive role of the MGMT status has been demonstrated when RT and concomitant TMZ were used in both young and elderly patients [21, 22]. Unfortunately, we did not have any information on the MGMT promoter methylation status of patients in our study because testing is not routinely performed in our institution. However, MGMT testing has not yet been validated in clinical practice due to the need for standardization of the available techniques [13, 23]. In the future, MGMT status should help

Table 2 Univariate analysis of overall survival, and progression-free survival

Characteristics	OS		PFS	
	Median months (95% CI)	p value	Median months (95% CI)	p value
Sex				
Male	14.0 (3.4–24.6)	0.95	7.3 (3.1–11.6)	0.28
Female	7.5 (2.0–13.1)		4.3 (2.1–6.5)	
Surgery				
Biopsy	5.8 (3.0–8.6)	0.16	4.3 (3.0-5.6)	0.07
Complete/partial resection	14.0 (0.1–28.8)		9.1 (5.5–12.7)	
Baseline KPS				
≤70	7.5 (NC–NC)	0.11	5.8 (NC–NC)	0.16
>70	8.2 (0.1–18.3)		5.8 (2.5–9.2)	
ConcurrentTMZ				
No	6.1 (2.1–10.1)	0.28	4.3 (1.0–7.6)	0.23
Yes	15.4 (0.1–34.3)		5.8 (3.1–8.6)	
Hospitalization				
No	12.2 (4.6–19.8)	**<0.01**	5.8 (3.3–8.4)	**0.02**
Yes	3.8 (2.8–4.8)		3.4 (2.1–4.7)	

Bold values are statistically significant

OS overall survival, *PFS* progression-free survival, *KPS* Karnofsky performance status, *TMZ* temozolomide

physicians in the selection of patients who may benefit from TMZ.

In our study 47.6% of patients were treated with concomitant TMZ but we did not observe any difference in terms of survival with or without the drug. Uzuka et al. found that the use of concomitant and/or adjuvant TMZ and postoperative KPS were independent predictors of survival on multivariate analyses in patients 76 or older (median 78 years) [19]. Minniti et al. treated 71 patient ≥70 years old with hypofractionated 3-week RT with concomitant and adjuvant TMZ in a phase II study and reported a median OS of 12.4 months [21]. In the subgroups analyses they reported a median OS of 11.4 and 12.7 months in patients ≥75 and <75 years old, respectively. In a recent retrospective study, the same authors compared clinical outcomes and toxicities in 243 patients ≥65 years old treated for GBM with standard or short-course RT plus TMZ using a propensity-matched analysis [24]. Interestingly, only 14% of patients treated with short course RT and TMZ experienced grade 2–3 neurologic adverse events. Moreover, patients in the short-course group had better KPS scores over time and required less increase in their daily dose of dexamethasone after treatment, as already described by Roa et al. [10]. In our study, only 38.1% of patients required the introduction or increase of steroids during RT, consistent with these studies. Despite these interesting results, no definite conclusions can be drawn. The EORTC 26062-22061/NCIC trial will attempt to answer the question of whether the addition of TMZ to short-course RT will confer survival advantage compared to short-course RT alone [14].

An essential issue to consider in the management of older patients is the preservation of quality of life. Treatment related toxicities may be particularly significant in elderly patients because of their initial performance status, with small decrements possibly leading to hospitalization. Recently, a retrospective cohort study among 5029 patients ≥65 years old with GBM using the SEER database found that 21% of all patients analysed were hospitalized for at least 30 cumulative days between diagnosis and death, and 22% spent at least one fourth of their remaining lives as inpatients [25]. Interestingly, they found that age was not associated with hospitalization burden, contrary to the age-related increase in patient comorbidities. They concluded that a definition of "elderly" goes beyond the chronological age and takes also into accounts the performance status. In our series, only three patients were hospitalised during RT because of a decline in overall status during treatment and four patients were admitted to our institution before starting the treatment. We showed that hospitalization is a prognostic factor for OS in patients over 80 old with GBM. Our results confirm that "very elderly" should not be defined using chronological age alone.

In the setting of limited survival, reducing the overall treatment time is an important consideration. The RT fractionation used in the present study is a 3-week schedule that represents a reasonable balance between overall treatment time, efficacy and toxicity, with particular regard to early-delayed encephalopathy, which can affect patients in the first 2 months after RT [26]. In a study of 158 patients, Wang et al. reported the same conclusions [27]. An additional improvement could be

Table 3 Series of elderly patients with glioblastoma

Study	n	KPS	Age criteria	RCT	Treatment	Age (median)	Median OS (months)
Roa et al. [10]	100	≥60	≥60	Yes	40/15	Mean 72.4	6.4
					60/30		5.9
Keime-Guibert et al. [9]	85	≥70	≥70	Yes	RT	73 (70–85)	7.2
					BSC		3
Malmström et al. [12]	342	0–2	≥60	Yes	60/30	NA	6
					34/10		7.5
					TMZ		8
Wick et al. [11]	584	≥60	≥65	Yes	60/30	NA	9.8
					TMZ		8.6
Minniti et al. [24]	127	≥60	≥60	No	40/15 + TMZ	NA	12
					60/30 + TMZ		12.5
Alvord et al. [25]	135	≥50	≥65	No	40/15	71 (65–85+)	4.1
					40/15 + TMZ		9.6
					60/30		9.5
					60/30 + TMZ		11.1
Uzuka et al. [19]	79	≥10	≥76	No	RT ± CHT[a]	78	11.8
					CHT		5.3
					TMZ ± RT		16.3
					No TMZ ± RT		7.1
Idbaih et al. [17]	28	≥70	≥70	No	40/15	74.6 (70.1–85.7)	50.6 weeks
Piccirilli et al. [18]	22	NA	≥80	No	RT + TMZ	83	13.7
Present study	21	≥60	≥80	No	40/15 ± TMZ	82 (80–88)	7.5

OS overall survival, *KPS* Karnofsky performance status, *TMZ* temozolomide, *CHT* chemotherapy, *RT* radiotherapy, *RCT* randomized controlled trial

[a]Administered chemotherapy regimen were TMZ or ACNU/MCNU

obtained using a shorter treatment like the one used in the trial from Malmström et al. In that study 2-week hypofractionated RT (34 Gy in ten fractions) was used [12]. Recently, Roa et al., in a phase III study, compared two regimens of 3D conformal RT for elderly and/or frail patients: a 3-week RT regimen (40 Gy in 15 fractions) vs. 1-week schedule (25 Gy in 5 fractions) [28]. They found no differences in OS, PFS and quality of life between the two RT regimens, concluding that the 1-week schedule may be recommended as a treatment option in these patients in view of the reduced overall treatment time.

There are several limitations to this study including the retrospective nature and the low number of patients assessed. In our series, only 47.6% of patients received combined RT and TMZ. Moreover, the use of concomitant TMZ was based on treating physician preference. Information about MGMT the methylation of our patients was not available.

Conclusions

We showed that a 3-week RT schedule is feasible with acceptable tolerance among "very elderly" patients affected by GBM. Patients 80 and older should be considered for management based on RT. Treatment decisions should include more than chronological age, considering the performance status of patients and their comorbidities. The results of the NCIC/EORTC trials may clarify the role of hypofractionated RT associated with concurrent TMZ, using MGMT status in patient selection.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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