

# Glioblastoma in the Elderly: The Impact of Advanced Age on Treatment and Survival

Giuseppe Mariniello<sup>1</sup> Carmela Peca<sup>1</sup> Marialaura Del Basso De Caro<sup>2</sup> Arcangelo Giamundo<sup>1</sup>  
Renato Donzelli<sup>1</sup> Francesco Maiuri<sup>1</sup>

<sup>1</sup>Department of Neurosciences, Neurosurgical Clinic, "Federico II" University School of Medicine, Napoli, Italy

<sup>2</sup>Department of Biomorphologic and Functional Sciences, Section of Pathology, "Federico II" University School of Medicine, Naples, Italy

Address for correspondence Giuseppe Mariniello, MD, PhD,

Department of Neurosciences, Neurosurgical Clinic, "Federico II" University School of Medicine, 5 Via S. Pansini, Naples 80131, Italy (e-mail: giumarin@unina.it).

J Neurol Surg A 2014;75:276–281.

## Abstract

**Objective** To evaluate the effects of combined treatments on the outcome and survival of elderly ( $\geq 65$  years) patients with glioblastoma as compared with younger ones.

**Material and Methods** Fifty consecutive elderly ( $\geq 65$  years) patients (group A) who underwent complete or subtotal ( $> 80\%$ ) resection of brain glioblastoma followed by irradiation and chemotherapy with temozolomide between 2004 and 2009 were retrospectively reviewed and compared with 50 glioblastoma patients aged  $< 65$  years, treated in the same period (group B). Patient sex, tumor location, size and side, combined treatments, reoperation, progression-free survival, and overall survival were compared in the two groups by using the Kaplan-Meier method.

**Results** There were no significant differences between the two groups for tumor location, size and side, and K<sub>i</sub>-67 Li. Forty-four of 50 group B patients were treated by the Stupp protocol, whereas all group A patients underwent irradiation and adjuvant temozolomide. Second-line chemotherapy was administered in 32% of group A and 76% of group B cases, and reoperation was performed in 16% and 36%, respectively. The median survival of the overall series of 100 patients was 15.6 months. Group A patients ( $\geq 65$  years) had a median survival of 14.5 months, significantly lower than group B cases (17 months) ( $p = 0.02$ ).

**Conclusion** Elderly patients with glioblastoma may benefit from combined treatments, including surgery, radiotherapy, and chemotherapy. Although younger patients do survive longer than older ones, the difference of survival is less significant if several criteria of selection to surgery, such as good Karnofsky performance status (KPS), largely resectable tumor, and no significant comorbidity, are respected.

## Keywords

- ▶ glioblastoma
- ▶ age
- ▶ elderly
- ▶ surgery

## Introduction

Glioblastoma is the most common primary brain tumor in adults, with a peak incidence between 65 and 74 years<sup>1</sup>; because of the higher median age of the general population, an increased incidence in older patients (up to 20% after 80 years) has been reported.<sup>2</sup>

In spite of the advancements in imaging, surgical techniques, and adjuvant treatments, the prognosis of glioblastoma remains dismal.<sup>3,4</sup> The two clinical parameters that are widely accepted as indicators of prolonged survival include a favorable ( $\geq 70$ ) Karnofsky performance status (KPS) and younger patient age at time of diagnosis.<sup>5</sup>

received  
August 30, 2012  
accepted after revision  
May 10, 2013  
published online  
January 4, 2014

© 2014 Georg Thieme Verlag KG  
Stuttgart · New York

DOI <http://dx.doi.org/10.1055/s-0033-1349713>.  
ISSN 2193-6315.

For these reasons, the age threshold between younger and adult patients, the management of glioblastoma in the elderly, and the influence of advanced age on outcome are still controversial.

The present report discusses the effect of combined treatments and the factors affecting the survival of elderly ( $\geq 65$  years) patients with glioblastoma as compared with younger ones. Its aim is also to determine whether combined treatments are advisable in older patients.

## Material and Methods

### Study Design

Fifty consecutive patients aged  $\geq 65$  years with newly diagnosed supratentorial glioblastoma, treated at the Neurosurgical Clinic of the "Federico II" University of Naples between 2004 and 2009, were reviewed (Group A). The data were compared with those of a group of 50 patients  $< 65$  years treated in the same period (Group B).

The inclusion criteria were a KPS  $> 70$ , complete or subtotal ( $> 80\%$ ) surgical resection, completed radiotherapy, and adjuvant and/or concomitant chemotherapy with temozolomide. Patients with multicentric tumors and gliomatosis, those who underwent biopsy or limited resection, those who died for unrelated conditions, and those lost to follow-up were excluded. Patients with significant comorbidities, including recent heart infarction, cardiac insufficiency, and kidney failure, were also excluded.

### Neuroradiological Assessment

Magnetic resonance (MR) studies before and after contrast administration were obtained preoperatively in all patients. Spectroscopic sequences were also performed in 63 cases. The volume of the initial tumor was defined by measuring the three main tumor diameters.

All patients were studied by computed tomography (CT) scan within 72 hours after surgery. MR before and after contrast administration was performed 1 month postoperatively. The residual tumor was defined as contrast enhancement and calculated as percentage of the initial tumor volume.

### Treatments

All 100 patients underwent complete or subtotal ( $> 80\%$ ) tumor resection. Locoregional chemotherapy with carmustine was used in the last 35 patients.

Adjuvant radiotherapy was administered in all patients with a total dose ranging between 54 and 60 Gy, with daily doses of 2 Gy. Temozolomide was used as concomitant and adjuvant therapy according to the Stupp<sup>6</sup> protocol (44 cases), or as adjuvant therapy only (56 cases). Adjuvant temozolomide was administered at doses of 300 mg/daily for 5 days every 28 days for at least 6 months or until to progression. Second-line chemotherapy with fotemustine or irinotecan was used at the tumor progression in 44 patients.

Twenty-six patients underwent reoperation for tumor regrowth.

### Follow-Up

In all patients clinical examination and postcontrast MR were performed 1 month after surgery, one month to 45 days after the end of the radiotherapy, and then every 3 months.

The data of the whole series were reviewed in December 2011 (follow-up of at least 2 years). For patients lost to follow-up, the family was contacted by phone. Patients who were still alive at last contact were surveyed for survival analysis.

### Bias Identification

Several factors affecting the outcome and survival were stratified into patients  $\geq 65$  years and patients  $< 65$  years. These include sex, tumor location and side, tumor size, type of adjuvant treatment, K<sub>i</sub>-67 Li, progression-free survival (PFS), reoperation, and overall survival.

### Statistical Analysis

The statistical analysis was performed by using the Kaplan-Meier method. A value  $< 0.05$  was considered as significant.

## Results (–Table 1)

The 100 patients of the overall series were 62 males and 38 females, ranging in age between 24 and 80 years (median age 61 years).

The two groups ( $\geq 65$  years and  $< 65$  years) did not show significant differences in patient sex, tumor location and side, tumor size, and K<sub>i</sub>-67/MIB-1 Li. Forty-four of 50 patients of Group B underwent irradiation with 60 Gy and concomitant (75 mg/day) and adjuvant temozolomide (Stupp protocol). Six patients of Group B and all of Group A underwent irradiation with 54 to 60 Gy and adjuvant temozolomide.

The treatments at tumor progression were as follows: second-line chemotherapy with fotemustine or irinotecan was administered in 44 patients, 16 (32%) of Group A and 38 (76%) of Group B. Among 26 patients undergoing reoperation after an interval of 7 to 40 months from the initial surgery, 8 (16%) belonged to Group A and 18 (36%) to Group B. Thus, the overall frequency of the treatments at progression was higher in younger than in elderly patients.

The median PFS of the overall series was 10 months, and the overall median survival was 15.6 months. The stratification of the outcome and survival according to the age was as follows: in Group A ( $\geq 65$  years) the median PFS was 8.4 months. In this group 41 patients died from tumor progression 4 to 42 months after surgery (median survival 14 months). Nine patients were still alive at 13 to 41 months (median survival 16 months). The median overall survival of this group was 14.5 months. It is noteworthy that three patients aged  $> 70$  years survived 39 to 42 months. There was no difference of survival in the different age group (65 to 70 years and  $> 70$  years).

In Group B ( $< 65$  years) the median PFS was 11.7 months. In this group 39 patients died from tumor progression 7 to 36 months after surgery (median survival 16.2 months). Eleven patients were still alive at 13 to 84 months (median survival 20 months). The three patients of the overall series

**Table 1** Distribution of clinicopathological features, treatments, and survival between younger and elderly patients in the present study

		Overall series	Group A ≥ 65 years	Group B < 65 years	p value
		100 pts	50 pts	50 pts	
Sex	F	38	18 (36%)	20 (40%)	n.s.
	M	62	32 (64%)	30 (60%)	
Tumor location	Frontal	28	16 (32%)	12 (24%)	n.s.
	Temporal	36	16 (32%)	20 (40%)	
	Parietal	26	12 (24%)	14 (28%)	
	Occipital	10	6 (12%)	4 (8%)	
Side	Left	52	20 (40%)	28 (56%)	n.s.
	Right	48	30 (60%)	22 (44%)	
Size (median)		34.0 cm <sup>3</sup>	35.7 cm <sup>3</sup>	32.2 cm <sup>3</sup>	n.s.
Ki-67 Li (median)		26%	24%	28%	n.s.
Adjuvant treatments	Locoregional carmustine therapy	35	21 (60%)	14 (40%)	
	RT + concomitant and adjuvant TMZ (Stupp protocol)	44	–	44 (88%)	
	RT + adjuvant TMZ	56	50 (100%)	6 (12%)	
	Second-line chemotherapy	44	16 (32%)	38 (76%)	
Reoperation		26	8 (16%)	18 (36%)	
PFS		10 months	8.4 months	11.7 months	0.02
Overall survival	Overall median survival	15.6 months	14.5 months	17 months	0.02
	Dead patients		14 months (41 pts)	16.2 months (39 pts)	
	Alive patients		16 months (9 pts)	20 months (11 pts)	

Abbreviations: F, female; M, male; n.s., not significant; PFS, progression-free survival; RT, radiotherapy; TMZ, temozolomide.

who survived more than 5 years belong to this group. The overall median survival of this group was 17 months.

The difference of PFS and overall median survival between the two groups is statistically significant ( $p = 0.02$ ).

## Discussion

Advanced patient age is a recognized factor of poor survival in patients with glioblastoma.<sup>5,7–9</sup> However, the incidence of malignant gliomas in the elderly population is very high.<sup>1,2</sup> Thus, the treatment modalities and the outcome of this age group are still discussed and remain controversial.

This retrospective study analyzes the outcome and survival in two groups of younger and older glioblastoma patients. Only three recent reports<sup>3,10,11</sup> have compared the outcome of younger and elderly patients harboring brain glioblastoma (– Table 2).

The age limit to consider a patient as elderly is variably defined, ranging in the literature studies from 60 to 70 years.<sup>3,4,10–16</sup> Despite the limited postoperative survival of patients with glioblastoma, even older individuals are expected to live long enough to benefit from the treatments. We think that 65 years may be considered an appropriate age limit.

In the reported series, the older age group often includes patients with different concomitant pathologies and different surgical risk. In our study we have excluded patients with significant comorbidities, which may influence survival. This could be a reason for a less significant difference of survival between younger and older patient in our series (– Table 2).

In this study several factors have been correlated with the outcome and survival of younger patients versus elderly patients with glioblastoma. There were no significant differences for tumor location, size, and proliferation index evaluated by Ki-67 Li MIB-1. The values of MIB-1 are rather variable in most series on glioblastoma and are unable to differentiate glioblastoma from anaplastic astrocytoma.<sup>17,18</sup> However, it seems to correlate with the survival of patients with glioblastoma but not with their age at diagnosis.

The significance of the type of surgery (complete resection, incomplete resection, and biopsy) was the focus in five series.<sup>4,10,12,13,19</sup> The completeness of the tumor resection was associated with significantly better median survival (5.7 to 17.3 months) than was incomplete resection (7 to 11 months) and biopsy (2.2 to 3.6 months). These data confirm that complete resection of the enhancing tumor must be performed, when possible, in elderly patients as well as for the whole population of patients with newly diagnosed

**Table 2** Differences of survival between younger and elderly patients in the present and other studies

Author	No. of pts	Age limit	Survival (younger, elderly)	p value
Stark et al (2007)	345	60 years	14 months, 8.4 months	0.0001
Stummer et al (2008)	243	60 years	14 months, 11 months	0.0090
Casartelli et al (2009)	196	64 years	13.6 months, 9.1 months	0.002
Present series	100	65 years	17 months, 14.5 months	0.02

glioblastoma multiforme.<sup>9,10,20</sup> To this end, fluorescence-guided resection with 5-aminolevulinic acid (ALA) may be helpful.<sup>10,21</sup>

The type of combined treatments is a key factor for the outcome. In nine series of elderly patients treated with variable entity of surgical resection (complete or incomplete), radiotherapy with variable radiation doses and chemotherapy in the pretemozolomide era,<sup>3,11–16,19,22</sup> the median survival ranged from 4.2 to 13 months, with only one series reporting a median survival of more than 1 year.<sup>22</sup> On the other hand, in seven series of elderly patients treated by complete or subtotal surgical resection, radiotherapy with 60 Gy, and adjuvant temozolomide,<sup>3,4,10,23–26</sup> (►Table 3) median survival ranged from 11 to 16.3 months, with only one series reporting a median survival of less than 1 year.<sup>24</sup>

The data from these studies confirm that radical surgical resection followed by a full course of radiotherapy and adjuvant temozolomide is the best treatment for elderly glioblastoma patients with good prognostic factors. We obtained in our series a median survival of 14.5 months. The combined treatment provides significant benefit over the survival compared with radiotherapy alone and significantly improves the time to progression compared with radiotherapy plus standard chemotherapy.<sup>15</sup>

The O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation is an important prognostic marker and has been consistently associated with newly diagnosed glioblastoma. However, its value in elderly patients is still unclear. Two studies<sup>27,28</sup> have shown that MGMT methylation is a favorable prognostic factor associated with significantly improved median survival in elderly patients. On the other hand, two other studies<sup>29,30</sup> did not show statistically significant

correlation. Further prospective studies are required to define the role of MGMT methylation as a prognostic marker and to determine its predictive value for responsiveness to temozolomide in elderly patients.

The opportunity of an aggressive treatment for tumor recurrence in the elderly is still debated. In a literature review by Barbagallo et al, the rate of reoperation for glioblastoma ranged from 10 to 30% and varied with patient age.<sup>31</sup> Some studies<sup>3,32</sup> reported significantly lower rate of reoperation for glioblastoma recurrence with advanced age (16% in older versus 36% in younger patients of our series). However, repeated surgery for recurrence seems to also be associated with improved survival in elderly patients,<sup>3</sup> particularly if combined with other postoperative salvage treatment modalities.<sup>33</sup> Although randomized trials and bias in patient selection are lacking, age alone should not exclude elderly patients from aggressive treatment at recurrence.

The difference of median survival between younger and elderly patients was significant in all three series that reported this finding<sup>3,10,11</sup> (p value from 0.002 to 0.0001) (►Table 2). In our series the overall survival of both groups was slightly higher than most literature data, and the difference between younger and older patients was less significant (p = 0.02). This is due to the patient selection (KPS > 70, complete or subtotal tumor resection, complete adjuvant treatments, exclusion of cases with significant comorbidities).

Several molecular genetic features were found to be associated with the age and outcome of patients with glioblastoma.<sup>34,35</sup> There is evidence of a relationship between epidermal growth factor receptor (EGFR) overexpression and better prognosis in the older age group<sup>34</sup> and different prognostic significance of alterations of p53, 1p, and p16 in

**Table 3** Survival of elderly patients with glioblastoma after complete or subtotal (≥ 80%) resection, RT, and TMZ

Author	No. of pts	Age limit	Median survival
Stark et al (2007)	123	≥ 60 years	15 months
Stummer et al (2008)	50	≥ 60 years	13.8 months
Combs et al (2008)	43	≥ 65 years	11 months
Brandes et al (2009)	58	≥ 65 years	13.7 months
Gerstner et al (2009)	35	≥ 70 years	16.2 months
Minniti et al (2010)	83	≥ 70 years	15.3 months
Ewelt et al (2010)	35	≥ 65 years	15 months
Present series	50	≥ 65 years	14.5 months

different age groups.<sup>35</sup> This may suggest different tumorigenic pathways of glioblastoma with age.

## Conclusions

Elderly patients may benefit for an as radical as possible surgical resection of brain glioblastoma followed by radiotherapy and adjuvant chemotherapy with temozolomide. This combined treatment should be reserved to patients with good KPS, no significant comorbidity, and largely resectable tumors. In this way, the difference of survival between older and younger patients is less significant.

### Conflict of Interest

None

## References

- Wrensch M, Minn Y, Chew T, Bondy M, Berger MS. Epidemiology of primary brain tumors: current concepts and review of the literature. *Neuro-oncol* 2002;4(4):278–299
- Greig NH, Ries LG, Yancik R, Rapoport SI. Increasing annual incidence of primary malignant brain tumors in the elderly. *J Natl Cancer Inst* 1990;82(20):1621–1624
- Stark AM, Hedderich J, Held-Feindt J, Mehdorn HM. Glioblastoma—the consequences of advanced patient age on treatment and survival. *Neurosurg Rev* 2007;30(1):56–61, discussion 61–62
- Ewelt C, Goepfert M, Rapp M, Steiger HJ, Stummer W, Sabel M. Glioblastoma multiforme of the elderly: the prognostic effect of resection on survival. *J Neurooncol* 2011;103(3):611–618
- Stark AM, Nabavi A, Mehdorn HM, Blömer U. Glioblastoma multiforme—report of 267 cases treated at a single institution. *Surg Neurol* 2005;63(2):162–169, discussion 169
- Stupp R, Mason WP, van den Bent MJ, et al; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005;352(10):987–996
- Davis FG, Freels S, Grutsch J, Barlas S, Brem S. Survival rates in patients with primary malignant brain tumors stratified by patient age and tumor histological type: an analysis based on Surveillance, Epidemiology, and End Results (SEER) data, 1973–1991. *J Neurosurg* 1998;88(1):1–10
- Scott JN, Newcastle NB, Brasher PM, et al. Long-term glioblastoma multiforme survivors: a population-based study. *Can J Neurol Sci* 1998;25(3):197–201
- Lacroix M, Abi-Said D, Fourney DR, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg* 2001;95(2):190–198
- Stummer W, Reulen HJ, Meinel T, et al; ALA-Glioma Study Group. Extent of resection and survival in glioblastoma multiforme: identification of and adjustment for bias. *Neurosurgery* 2008;62(3):564–576, discussion 564–576
- Casartelli G, Dorcaratto A, Ravetti JL, et al. Survival of high grade glioma patients depends on their age at diagnosis. *Cancer Biol Ther* 2009;8(18):1719–1721
- Kelly PJ, Hunt C. The limited value of cytoreductive surgery in elderly patients with malignant gliomas. *Neurosurgery* 1994;34(1):62–66, discussion 66–67
- Mohan DS, Suh JH, Phan JL, Kupelian PA, Cohen BH, Barnett GH. Outcome in elderly patients undergoing definitive surgery and radiation therapy for supratentorial glioblastoma multiforme at a tertiary care institution. *Int J Radiat Oncol Biol Phys* 1998;42(5):981–987
- Whittle IR, Basu N, Grant R, Walker M, Gregor A. Management of patients aged >60 years with malignant glioma: good clinical status and radiotherapy determine outcome. *Br J Neurosurg* 2002;16(4):343–347
- Brandes AA, Vastola F, Basso U, et al. A prospective study on glioblastoma in the elderly. *Cancer* 2003;97(3):657–662
- Iwamoto FM, Cooper AR, Reiner AS, Nayak L, Abrey LE. Glioblastoma in the elderly: the Memorial Sloan-Kettering Cancer Center Experience (1997–2007). *Cancer* 2009;115(16):3758–3766
- Johannessen AL, Torp SH. The clinical value of Ki-67/MIB-1 labeling index in human astrocytomas. *Pathol Oncol Res* 2006;12(3):143–147
- Uehara K, Sasayama T, Miyawaki D, et al. Patterns of failure after multimodal treatments for high-grade glioma: effectiveness of MIB-1 labeling index. *Radiat Oncol* 2012;7:104
- Vuorinen V, Hinkka S, Färkkilä M, Jääskeläinen J. Debulking or biopsy of malignant glioma in elderly people - a randomised study. *Acta Neurochir (Wien)* 2003;145(1):5–10
- Keles GE, Anderson B, Berger MS. The effect of extent of resection on time to tumor progression and survival in patients with glioblastoma multiforme of the cerebral hemisphere. *Surg Neurol* 1999;52(4):371–379
- Pichlmeier U, Bink A, Schackert G, Stummer W; ALA Glioma Study Group. Resection and survival in glioblastoma multiforme: an RTOG recursive partitioning analysis of ALA study patients. *Neuro-oncol* 2008;10(6):1025–1034
- Pierga JY, Hoang-Xuan K, Feuvret L, et al. Treatment of malignant gliomas in the elderly. *J Neurooncol* 1999;43(2):187–193
- Brandes AA, Franceschi E, Tosoni A, et al. Temozolomide concomitant and adjuvant to radiotherapy in elderly patients with glioblastoma: correlation with MGMT promoter methylation status. *Cancer* 2009;115(15):3512–3518
- Combs SE, Wagner J, Bischof M, et al. Postoperative treatment of primary glioblastoma multiforme with radiation and concomitant temozolomide in elderly patients. *Int J Radiat Oncol Biol Phys* 2008;70(4):987–992
- Gerstner ER, McNamara MB, Norden AD, Lafrankie D, Wen PY. Effect of adding temozolomide to radiation therapy on the incidence of pseudo-progression. *J Neurooncol* 2009;94(1):97–101
- Minniti G, Amelio D, Amichetti M, et al. Patterns of failure and comparison of different target volume delineations in patients with glioblastoma treated with conformal radiotherapy plus concomitant and adjuvant temozolomide. *Radiation Oncol* 2010;97(3):377–381
- Gerstner ER, Yip S, Wang DL, Louis DN, Iafrate AJ, Batchelor TT. Mgmt methylation is a prognostic biomarker in elderly patients with newly diagnosed glioblastoma. *Neurology* 2009;73(18):1509–1510
- Ang C, Guiot MC, Ramanakumar AV, Roberge D, Kavan P. Clinical significance of molecular biomarkers in glioblastoma. *Can J Neurol Sci* 2010;37(5):625–630
- Costa BM, Caeiro C, Guimarães I, et al. Prognostic value of MGMT promoter methylation in glioblastoma patients treated with temozolomide-based chemoradiation: a Portuguese multicentre study. *Oncol Rep* 2010;23(6):1655–1662
- Abhinav K, Aquilina K, Gbejuade H, La M, Hopkins K, Iyer V. A pilot study of glioblastoma multiforme in elderly patients: treatments, O-6-methylguanine-DNA methyltransferase (MGMT) methylation status and survival. *Clin Neurol Neurosurg* 2013;115(8):1375–1378
- Barbagallo GM, Jenkinson MD, Brodbelt AR. 'Recurrent' glioblastoma multiforme, when should we reoperate? *Br J Neurosurg* 2008;22(3):452–455

- 32 Helseth R, Helseth E, Johannesen TB, et al. Overall survival, prognostic factors, and repeated surgery in a consecutive series of 516 patients with glioblastoma multiforme. *Acta Neurol Scand* 2010;122(3):159–167
- 33 Mandl ES, Dirven CM, Buis DR, Postma TJ, Vandertop WP. Repeated surgery for glioblastoma multiforme: only in combination with other salvage therapy. *Surg Neurol* 2008;69(5):506–509, discussion 509
- 34 Simmons ML, Lamborn KR, Takahashi M, et al. Analysis of complex relationships between age, p53, epidermal growth factor receptor, and survival in glioblastoma patients. *Cancer Res* 2001;61(3):1122–1128
- 35 Batchelor TT, Betensky RA, Esposito JM, et al. Age-dependent prognostic effects of genetic alterations in glioblastoma. *Clin Cancer Res* 2004;10(1 Pt 1):228–233