Glioblastoma in the elderly: treatment patterns and survival

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Practice points

- We conducted a retrospective review of the California Cancer Registry to examine treatment patterns and survival in elderly patients with glioblastoma.
- The optimal treatment regimen for elderly patients has not yet been established.
- For all treatment modalities, elderly patients (>70 years of age) had a lower median overall survival (OS) when compared with younger patients (18–70 years of age).
- Elderly patients were less likely to receive surgery plus radiation and chemotherapy.
- The extent of resection in elderly patients was less than in their younger counterparts.
- However, elderly patients had the greatest OS with surgery, radiation and chemotherapy.
- OS in some elderly patients may be improved by more extensive therapy, but needs to be evaluated prospectively.

Aim: The optimal treatment for elderly glioblastoma patients is unclear. We conducted a retrospective review of the California Cancer Registry to examine treatment patterns and survival by age. **Methods:** We identified 2670 adult patients from the California Cancer Registry with glioblastoma. We compared the extent of resection, treatment type and modality. **Results:** Elderly patients had the greatest overall survival (OS) with combined surgery, radiation and chemotherapy. However, they were more likely to undergo biopsy and less likely to receive combined radiation and chemotherapy than patients <70. **Conclusion:** OS was maximized in elderly patients who were able to get some surgical resection and undergo combined radiation and chemotherapy. OS survival in some elderly patients may be improved by more extensive therapy.

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Glioblastoma is the most common adult primary malignant brain tumor [1]. The median age at diagnosis is 64 years with a peak incidence in patients aged 75–84 years, numbers which are expected to further increase as the aging population expands [2,3]. Gliomas account for half of all intrinsic brain tumors. WHO grade IV glioblastomas are the most malignant variant and make up around half of all gliomas [4]. According to the Central Brain Tumor Registry of the United States, the 5-year survival rate for glioblastoma, between 2007 and 2011, is limited to 5%. The current standard of care is surgical resection plus concurrent radiation and chemotherapy with temozolomide, which provides a modest 14.6-month median survival [5,6]. Survival in the elderly

KEYWORDS

- California cancer registry
- chemotherapy • elderly
- glioblastoma • overall survival • radiation
- retrospective study
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is even shorter and usually limited to no longer than 8.5 months on average [6,7]. Despite a great effort in basic and clinical research, prognosis remains poor [6]. Prior to 2005, the standard of care for glioblastoma was a 6-week course of fractionated radiotherapy only. Starting in 2005, the standard of care shifted to radiation plus temozolomide chemotherapy, based on a randomized clinical trial by Stupp *et al.*

Surgery provides a histological diagnosis, can help with preservation of neurological function and improve survival [8]. Postoperative radiotherapy and chemotherapy improve overall and disease-free survival, with targeted therapies being trialed to improve the poor median survival [9,10]. The Stupp trial demonstrated an increase in median OS from 12.1 months with radiation only to 14.6 months with the addition of temozolomide, with an increase in 5-year survival of nearly 10% [5]. However, the Stupp study excluded patients aged >70 years. Therefore, it has not been rigorously determined whether such patients benefit from this treatment [11]. More aggressive tumor behavior, less aggressive treatments, increased toxicity, decreased tolerability and additional medical comorbidities could explain a higher severity of the disease in the elderly. The balance between treatment efficacy and quality of life is a major focus because of the shorter life expectancy of patients [12]. As the population continues to age, it is increasingly important to ensure the elderly are managed appropriately, with best possible treatment outcomes.

Many clinical trials in glioblastoma exclude the elderly and the optimal treatment approach for elderly glioblastoma patients has not yet been clearly established [13,14]. In addition, due to factors such as poorer prognosis associated with older age and the presence of other comorbidities, elderly glioblastoma patients are often treated with less aggressive, alternative regimens that may be better tolerated. There is no current standard of care for the treatment of the elderly with glioblastoma, and multiple abbreviated regimens have been developed based on the results of recent trials in frail or elderly glioblastoma patients [4,15–17]. Increasing age is associated with decreasing benefit from chemotherapy and an increasing risk of cognitive side effects from cranial irradiation [5,18]. Some studies have shown that elderly patients are often unable to complete the standard radiotherapy regimen of 6 weeks. A 6-week

radiotherapy regimen, therefore, may be associated with substantial risks of morbidity and early discontinuation [19]. Moreover, the tolerability of combined radiotherapy and temozolomide seems to be reduced in the elderly [20]. However, other studies have shown that age in itself is not a contraindication to chemotherapy and recent trials for glioblastoma in the elderly have not included a combined radiation and chemotherapy arm [2]. *MGMT* promoter methylation was shown to be a prognostic marker of outcome, and a strong predictor of benefit with temozolomide chemotherapy in elderly patients [4,11,19,21,22]. The overall survival seems to be significantly longer in elderly patients treated with temozolomide and who had methylated *MGMT* promoter status than in those who did not have *MGMT* promoter methylation [19]. To help understand treatment patterns of elderly individuals with glioblastoma, as well as outcomes, we retrospectively explored the treatment options, extent of surgical resection and survival for glioblastoma in the elderly in the post-temozolomide era, using the California Cancer Registry (CCR).

Materials & methods

• Data source

CCR is the State of California population-based cancer surveillance system. The CCR collects information about all cancers diagnosed in California (except basal and squamous cell carcinoma of the skin and carcinoma *in situ* of the cervix). Data for this retrospective study were obtained from CCR at UC San Diego Moores Cancer Center. In the study, we included a cohort containing patients diagnosed with glioblastoma grade 4 from 2005 to 2010 from all the institutions throughout the state of California reporting to CCR.

• Cohort selection

From the CCR data, we extracted patients with histologic codes 9380/3, 9381/3, 9382/3, 9400/3, 9401/3, 9440/3, 9441/3 and 9442/3. The date of diagnosis and the age at diagnosis were noted along with overall survival (in months). A total of 31,746 patients with a diagnosis of glioma were identified. From those, 12,040 were grade 4 and 2797 were diagnosed from 2005 to December 2010, with 2702 aged 18 years or older. A total of 32 (1.2%) patients had incomplete data with regard to type of treatment or extent of resection, and were excluded from

Figure 1. Search strategy.

Dx: Diagnosis.

the analysis. Finally, 2670 patients were retained for subsequent analysis with 1960 (73.4%) aged 70 years or younger and 710 (26.6%) older than 70 years of age (Figure 1). Patients were categorized in eight treatment groups: biopsy only, surgery only, biopsy plus chemotherapy, biopsy plus radiation, surgery plus chemotherapy, surgery plus radiation, biopsy plus chemotherapy and radiation and surgery plus chemotherapy and radiation. Extent of resection was then categorized into three types: biopsy, subtotal resection (STR) and gross total resection (GTR).

• Statistical analysis

OS was calculated from the date of diagnosis to either death or censored at 31 December 2010. Survival probability was compared by the Kaplan–Meier method with a log-rank test. Pairwise comparisons were conducted to analyze the association between OS and age groups. A Bonferroni pairwise comparison test was used to test the association between the median survival times and the Chi-square test to compare

the treatment options across the age groups. All analyses were performed with SAS Software. Differences were defined as statistically significant if $p < 0.05$.

Results

We first examined the type of treatment patients received, both as a whole group and then as a function of age. We assigned patients to one of eight treatment groups as outlined in the Methods. There were 2670 evaluable patients. A total 275 (10.3%) patients received no treatment for their tumors following biopsy diagnosis; 416 (15.6%) patients were treated only with surgery; 20 (0.7%) patients were treated with biopsy and chemotherapy; 96 (3.6%) patients were treated with biopsy and radiation; 76 (2.8%) were treated with surgery and chemotherapy; 211 (7.9%) were treated with surgery and radiation; 370 (13.9%) were treated with biopsy, radiation and chemotherapy; 1206 (45.2%) were treated with surgery, radiation and chemotherapy (Table 1). Next we stratified

Table 1. Type of treatment by age.			
	Age: 18–70 years (n [%])	Age: >70 years (n [%])	p-value
All patients (n = 2670)	1960 (73.4)	710 (26.6)	–
Biopsy only (n = 275)	148 (7.6)	127 (17.9)	<0.0001
Surgery only (n = 416)	252 (12.9)	164 (23.1)	<0.0001
Biopsy + chemotherapy (n = 20)	12 (0.6)	8 (1.1)	0.1731
Biopsy + radiation (n = 96)	50 (2.5)	46 (6.5)	<0.0001
Surgery + chemotherapy (n = 76)	53 (2.7)	23 (3.2)	0.4624
Surgery + radiation (n = 211)	150 (7.7)	61 (8.6)	0.4271
Biopsy + chemotherapy + radiation (n = 370)	279 (14.2)	91 (12.8)	0.3488
Surgery + chemotherapy + radiation (n = 1206)	1016 (51.8)	190 (26.8)	<0.0001

by age, and found that the elderly patients were less likely to receive the full treatment regimen of surgery/radiation/chemotherapy as often as the younger group. Of the total number of 1960 patients aged 18–70, 1016 (51.8%) were treated with surgery, radiation and chemotherapy whereas only 190 (26.8%) aged >70 received this treatment regimen ($p < 0.0001$) (Table 1).

Next we evaluated OS. The median OS for all 2670 patients was 9 months (95% CI: 8–9 months). The median survival for patients aged 18–70 was 12 months (95% CI: 11–13 months). For patients >70 years of age,

the median survival was 4 months (Figure 2). We compared the OS for the eight subgroups based on treatment modality and age (Table 2). In both age groups, OS was shortest with biopsy/surgery alone, improved with radiation and the greatest with radiation and chemotherapy combined. For patients aged 18–70, the median OS was 2 months (95% CI: 1–2 months) for biopsy only, 4 months (95% CI: 3–5 months) for surgery only, 7 months (95% CI: 5–16 months) for biopsy and radiation, 11 months (95% CI: 10–14 months) for surgery and radiation, 9 months (95% CI: 8–12 months) for biopsy, radiation and

Figure 2. Kaplan–Meier analysis of overall survival for the two age groups. The median survival for the 18–70 group is 12 months and the median survival for the >70 group is 4 months. OS: Overall survival.

Table 2. Median overall survival (months) by age and treatment modality.

	Age: 18–70 years (n = 1960)	Age: >70 years (n = 710)	p-value
All patients (n = 2670)	12.0	4.0	
Biopsy only (n = 275)	2.0	2.0	1.0000
Surgery only (n = 416)	4.0	3.0	0.0419
Biopsy + chemotherapy (n = 20)	5.0	4.5	1.0000
Biopsy + radiation (n = 96)	7.0	3.0	0.0139
Surgery + chemotherapy (n = 76)	16.0	5.0	0.8383
Surgery + radiation (n = 211)	11.0	5.0	0.0005
Biopsy + chemotherapy + radiation (n = 370)	9.0	6.0	1.0000
Surgery + chemotherapy + radiation (n = 1206)	16.0	8.0	<0.0001

chemotherapy and 16 months (95% CI: 15–17 months) for surgery, radiation and chemotherapy (Figure 3). For patients >70, the median OS was 2 months (95% CI: 1–2 months) for biopsy only, 3 months (95% CI: 2–3 months) for surgery only, 3 months (95% CI: 2–4 months) for biopsy and radiation, 5 months (95% CI: 4–6 months) for surgery and radiation, 6 months (95% CI: 5–7 months) for biopsy, radiation and chemotherapy and 8 months (95% CI: 7–9 months) for surgery, radiation and chemotherapy (Figure 4).

In order to make comparisons with published data from previous studies, we calculated the median OS for the combined groups biopsy/surgery and radiation, and biopsy/surgery with radiation and chemotherapy. For patients aged 18–70,

the median OS biopsy/surgery followed by radiation was 11 months (95% CI: 10–14 months) and 14 months (95% CI: 13–15 months) for biopsy/surgery with radiation and chemotherapy. For patients >70, the median OS was 5 months (95% CI: 4–6 months) for biopsy/surgery and radiation, and 7 months (95% CI: 6–8 months) for biopsy/surgery, radiation and chemotherapy.

We then evaluated the effect of extent of resection on survival for each age group. Extent of resection was categorized into biopsy only, STR and GTR. In the younger patients, OS was significantly improved with more extensive resection. For patients aged 18–70, the median OS was 6 months (95% CI: 5–7 months) for biopsy, 12 months (95% CI: 11–14 months) for STR and 16 months (95% CI: 15–18 months)

Figure 3. Overall survival by treatment type for the 18–70 group. OS is improved with additional treatment modalities.

OS: Overall survival.

Table 3. Extent of resection by age.

	Age: 18–70 years (n [%])	Age: >70 years (n [%])	p-value
Biopsy (n = 761)	489 (24.9)	272 (38.3)	<0.0001
STR (n = 1148)	878 (44.8)	270 (38.0)	0.0018
GTR (n = 761)	593 (30.3)	168 (23.7)	0.0009

GTR: Gross total resection; STR: Subtotal resection.

for GTR (Figure 5). Elderly patients had a longer OS with at least some type of surgical resection (STR or GTR) when compared with biopsy only. However, there was no significant difference in OS between STR and GTR in the elderly. For patients >70, the median OS was 3 months (No CI) for biopsy, 5 months (95% CI: 4–6 months) for STR and 6 months (95% CI: 5–6 months) for GTR (Figure 6).

Next, we determined if there were differences in the extent of resection as a function of age (Table 3). The elderly patients were more likely to receive only a diagnostic biopsy when compared with the younger group, who were more likely to undergo more extensive surgery. Of the total number of 710 patients aged >70, 272 (38.3%) got a diagnostic biopsy only whereas 489 (24.9%) of the patients aged 18–70 got a diagnostic biopsy, which was statistically significant (p-value < 0.0001) (Table 3). Elderly patients had a longer OS with at least some type of surgical resection (STR or GTR) instead of biopsy only (5 and 6 months for STR and GTR compared

with 3 months for biopsy), even though they were less likely to receive a resection (Table 4).

Discussion

The survival data reported in our study are consistent with other published retrospective and prospective studies in glioblastoma. In our study, the median survival for patients in the 18–70 group who were treated with biopsy or surgery and followed by radiation and chemotherapy was 14 months, compared with 14.6 months in Stupp trial [13]. For patients receiving biopsy/surgery and radiation, we reported a median OS of 11 months compared with 12.1 months in the Stupp trial [13]. In the >70 group, the median OS in the radiation only group was 5 months, similar to the median OS in the Nordic trial of 5.2 months for patients that were >70 and received 60 Gy of radiation [19]. The OS for patients treated with surgery only was 3 months in our study, compared with the 2 months of OS found in Burton *et al.* study [14].

Figure 4. Overall survival by treatment type for the >70 group. OS is improved with additional treatment modalities. OS: Overall survival.

Table 4. Median overall survival (months) by age and extent of surgery.

	Age: 18–70 years (n = 1960)	Age: >70 years (n = 710)	p-value
Biopsy (n = 761)	6.0	3.0	0.0013
STR (n = 1148)	12.0	5.0	<0.0001
GTR (n = 761)	16.0	6.0	<0.0001

GTR: Gross total resection; STR: Subtotal resection.

For all the treatment options analyzed, the elderly patients (>70) had a lower median OS when compared with the younger group (18–70). Despite this poor prognosis, their median OS was maximal with combined surgery, radiation and chemotherapy. For elderly patients who underwent surgical resection, the median survival was 3 months. With the addition of radiotherapy, median survival increased to 5 months and when chemotherapy was also added to the regimen, the median survival was 8 months. However, elderly patients were significantly less likely to undergo full treatment regimen of surgery plus radiation and chemotherapy when compared with younger patients. In the 18–70 group, 51.8% were treated with a regimen of surgery, radiation and chemotherapy, whereas only 26.8% in the >70 group received the full treatment regimen. The same held true for extent of resection, where 38.3% of elderly

patients received a biopsy as opposed to surgical resection, compared with only 24.9% of younger patients. Elderly patients were less likely to receive either GTR or STR when compared with their younger counterparts. Elderly patients had a longer median survival with at least some type of surgical resection (STR or GTR) instead of biopsy only, even though they were less likely to receive a resection. Interestingly, there were no differences in OS between STR and GTR in patients >70. For elderly patients able to undergo at least partial resection, there may be a survival benefit, and attempting to achieve a GTR in the elderly may not provide an additional benefit over partial debulking surgery.

As with all retrospective studies and epidemiological registries, there are a number of inherent limitations. Retrospective analysis of registry data is limited by the variables collected by the registry. Specific data on radiation

Figure 5. Overall survival by extent of resection for the 18–70 group. OS is significantly improved with more surgery: biopsy (6 months), STR (12 months) and GTR (16 months).

GTR: Gross total resection; OS: Overall survival; STR: Subtotal resection.

dose, chemotherapy type or performance status were not extractable variables. In our review, 32 patients were removed from the study because of incomplete data with regard to type of treatment or extent of surgery. In the CCR, the diagnosing institution is responsible for subsequent data collection, even if the patients go elsewhere for treatment. This requires diligent follow-up and voluntary participation from other institutions or community-based practitioners. Because neuro-oncology is highly subspecialized, we suspect that many patients receive initial diagnosis in a community hospital setting and are subsequently transferred to tertiary care centers for further surgery, radiation or chemotherapy, leading to inaccurate or incomplete treatment data collection. For instance, a small percentage of patients (2.8%) reportedly received surgery and chemotherapy without radiation, yet in the 18–70 group had a median OS that was similar to those treated with radiation and chemotherapy. Similarly, we originally planned to examine differences in treatment patterns between academic institutions and other California hospitals, but such a comparison would be highly confounded by crossover among institutions.

Recent prospective studies of glioblastoma in the elderly have included a chemotherapy only arm with temozolomide, and have shown that chemotherapy only was better than radiotherapy only, but only in patients with *MGMT* promoter methylation [4,19]. Information on *MGMT* promoter methylation status was not available to us in the registry, nor was data on initial performance status. Some recent prospective trials of the elderly have also stratified by performance status, whereas our study included all patients. Furthermore, there is also no set definition of ‘elderly.’ The Stupp trial included patients aged 18–70 and a WHO performance status 0–2. NOA-08 included patients >65 years old but also with a Karnofsky performance status >60. The Nordic trial included patients >60 years old with a WHO performance status 0–2 [19]. The IAEA study evaluated both elderly and/or frail patients, including patients as young as 50, and with a performance status as low as 50% [23]. Based on the age cutoff of 70 in the Stupp study, and the subgroup analysis for patients >70 years old in the Nordic trial, we used a definition of elderly as >70 years old for this study. We were unable to evaluate the impact of performance status, which may have explained why elderly patients

Figure 6. Overall survival by extent of resection for the >70 group. OS for biopsy (3 months) is inferior to STR (5 months) or GTR (6 months). There was no significant difference in overall survival between STR and GTR in patients.

GTR: Gross total resection; OS: Overall survival; STR: Subtotal resection.

were more likely to get a biopsy instead of resection or to be treated with radiation instead of radiation and chemotherapy. However, there is considerable heterogeneity among the ‘elderly’ population, and all of these definitions are not without their limitations. Certainly, age, performance status, molecular phenotype and medical co-morbidities will likely factor into how this population is ultimately treated in the future.

For our study, we restricted our initial search to the years of 2005–2010, starting with the year of the Stupp study and when the addition of temozolomide to radiation became the current standard of care. We included all patients up through 2010, which is the most recent data in the CCR. Although the CCR data do not specify the type of chemotherapy, we assumed that patients received standard of care temozolomide, which is supported by the fact that the OS in our analysis is similar to the OS of other upfront studies, including the Stupp trial. Despite these limitations, our study shows that elderly patients may benefit from surgical debulking followed by combined radiation and chemotherapy.

A previous study evaluated the treatment patterns of patients >65 years of age with glioblastoma, from 1994 to 2002, using the Survival Epidemiology and End Results (SEER) database [24]. The SEER study evaluated the pretemozolomide era, in contrast to our study which was limited to the post-temozolomide era. In the SEER study, 55% of patients received radiation alone, and 10% received radiation and chemotherapy. This is in contrast to our more recent analysis, in which 15% of patients in the >70 cohort received radiation alone and 40% received radiation and chemotherapy. The rates of no radiation or chemotherapy were 35 versus 39%, respectively. 61% of patients in both studies underwent at least partial resection, although our population was slightly older. While the approval of temozolomide chemotherapy has increased the fraction of patients who receive chemotherapy, the rates for surgery and overall treatment were largely unchanged.

Recently completed trials in the elderly have not included a combined radiation and chemotherapy arm. A randomized Phase III study of

temozolomide and short-course radiation versus short-course radiation alone in newly diagnosed elderly glioblastoma patients is currently underway to answer that question (Canadian Cancer Trials Group CE.6). Elderly was defined as age >65 and a WHO performance status of 0–2. Preliminary data showed a median OS of 7.6 months in the RT group and 9.3 months in the RT/TMZ group [25]. Quality of Life measures were not different between the two groups, suggesting that the addition of chemotherapy was well tolerated. With regards to our data, this suggests that the improvement in OS with more treatment is likely due to an improvement in efficacy and not merely more favorable prognostic factors. However, the optimal treatment for all elderly patients, and especially those with poor performance status, which were not included in CE.6, remains to be determined, and more prospective trials are needed to establish the optimal therapy for all elderly patients with glioblastoma.

Conclusion

The treatment of elderly patients with glioblastoma is not yet optimized. Our data suggest that elderly patients demonstrate an improved overall survival with surgical debulking followed by radiation and chemotherapy, although the elderly are less likely to receive this combination when compared with their younger counterparts. Additional variables such as *MGMT* promoter methylation status or performance status may help define subgroups of elderly patients that could benefit from combined surgery, radiation and chemotherapy, and this needs to be studied prospectively.

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References

- 1 Cheo ST, Lim GH, Lim HC. Glioblastoma multiforme outcomes of 107 patients treated in two local institutions. *Singapore Med. J.* doi:10.11622/smedj.2016044 (2016) (Epub ahead of print).
- 2 Cannon FV, Rosenthal MA, Drummond K. Glioblastoma multiforme in the very elderly. *Neurosurg. Rev.* 39(1), 55–61 (2016).
- 3 Nghiemphu P, Cloughesy T. Glioblastoma therapy in the elderly: one age does not fit all. *Lancet Oncol.* 13(9), 857–858 (2012).
- 4 Wick W, Platten M, Meisner C *et al.* Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, Phase 3 trial. *Lancet Oncol.* 13, 707–715 (2012).

- 5 Stupp R, Hegi ME, Mason WP *et al.* Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised Phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol.* 10, 459–466 (2009).
- 6 Delgado-Lopez PD, Corrales-Garcia EM. Survival in glioblastoma: a review on the impact of treatment modalities. *Clin. Transl. Oncol.* (2016) (Epub ahead of print).
- 7 Scott JG, Bauchet L, Fraum TJ *et al.* Recursive partitioning analysis of prognostic factors for glioblastoma patients aged 70 years or older. *Cancer* 118, 5595–5600 (2012).
- 8 Kuhn D, Becker A, Ganslandt O, Bauer M, Buchfelder M, Nimsy C. Correlation of the extent of tumor volume resection and patient survival in surgery of glioblastoma multiforme with high-field intraoperative MRI guidance. *Neuro Oncol.* 13(12), 1339–1348 (2011).
- 9 Keime-Guibert F, Chinot O, Taillandier L *et al.* Radiotherapy for glioblastoma in the elderly. *N. Engl. J. Med.* 356, 1527–1535 (2007).
- 10 Minitti G, Muni R, Lanzetta G *et al.* Chemotherapy for glioblastoma: current treatment and future perspectives for cytotoxic and targeted agents. *Anticancer Res.* 29(12), 5171–5184 (2009).
- 11 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* 115, 3512–3518 (2009).
- 12 Biau J, Dalloz P, Durando X *et al.* Elderly patients with glioblastoma: state of the art. *Bull. Cancer* 102(3), 277–286 (2015).
- 13 Stupp R, Mason WP, van den Bent MJ *et al.* Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N. Engl. J. Med.* 352, 987–996 (2005).
- 14 Burton E, Ugiliweneza B, Woo S, Skirboll S, Boaky M. A surveillance, epidemiology and end results-medicare data analysis of elderly patients with glioblastoma multiforme: treatment patterns, outcomes and cost. *Mol. Clin. Oncol.* 3(5), 971–978 (2015).
- 15 Arvold ND, Reardon DA. Treatment options and outcomes for glioblastoma in the elderly patient. *Clin. Interv. Aging* 9, 357–367 (2014).
- 16 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.* 70, 987–992 (2008).
- 17 Keime-Guibert F, Chinot O, Taillandier L *et al.* Radiotherapy for glioblastoma in the elderly. *N. Engl. J. Med.* 356, 1527–1535 (2007).
- 18 Weller M, Platten M, Roth P, Wick W. Geriatric neuro-oncology: from mythology to biology. *Curr. Opin. Neurol.* 24, 599–604 (2011).
- 19 Malmström A, Grønberg BH, Marosi C *et al.* Nordic Clinical Brain Tumour Study Group (NCBTSG): temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, Phase 3 trial. *Lancet Oncol.* 13, 916–926 (2012).
- 20 Sijben AE, McIntyre JB, Roldan GB *et al.* Toxicity from chemoradiotherapy in older patients with glioblastoma multiforme. *J. Neurooncol.* 89, 97–103 (2008).
- 21 Hegi ME, Diserens AC, Gorlia T *et al.* *MGMT* gene silencing and benefit from temozolomide in glioblastoma. *N. Engl. J. Med.* 352, 997–1003 (2005).
- 22 Gallego Perez-Larraya J, Ducray F, Chinot O *et al.* Temozolomide in elderly patients with newly diagnosed glioblastoma and poor performance status: an ANOCEF Phase II trial. *J. Clin. Oncol.* 29, 3050–3055 (2011).
- 23 Roa W, Kepka L, Kumar N *et al.* International Atomic Energy Agency randomized Phase III study of radiation therapy in elderly and/or frail patients with newly diagnosed glioblastoma multiforme. *J. Clin. Oncol.* 33(35), 4145–4150 (2015).
- 24 Iwamoto FM, Reiner AS, Panageas KS *et al.* Patterns of care in elderly glioblastoma patients. *Ann. Neurol.* 64(6), 628–634 (2008).
- 25 Perry JR, Laperriere N, O'Callaghan CJ *et al.* A Phase III randomized controlled trial of short-course radiotherapy with or without concomitant and adjuvant temozolomide in elderly patients with glioblastoma (CCTG CE.6, EORTC 26062–22061, TROG 08.02, NCT00482677). *J. Clin. Oncol.* 34(Suppl.), Abstract LBA2 (2016).