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CLINICAL-PATIENT STUDIES

# Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma in elderly patients

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**Abstract** *Objectives* The optimal treatment for elderly patients (age > 70 years) with glioblastoma remains controversial. We conducted a prospective trial in 32 consecutive elderly patients with glioblastoma who underwent surgery followed by radiotherapy (RT) plus concomitant and adjuvant temozolomide. *Patients and Methods* 32 patients 70 years of age or older with a newly diagnosed glioblastoma and a Karnofsky performance status (KPS) ≥ 70 were treated with RT (daily fractions of 2 Gy for a total of 60 Gy) plus temozolomide at the dose of 75 mg/m$^2$ per day followed by six cycles of adjuvant temozolomide (150–200 mg/m$^2$ for 5 days during each 28-day cycle). The primary endpoint was overall survival (OS). Secondary endpoints included progression free survival (PFS) and toxicity. *Results* The median OS was 10.6 months and the median PFS was 7 months. The 6-month and 12-month survival rates were 91% and 37%, respectively. The 6-month and 12-month PFS rates were 56% and 16%, respectively. In multivariate analysis KPS was the only significant independent predictive factor of survival ($P = 0.01$). Adverse effects were mainly represented by neurotoxicity (40%), which resolved in most cases with the use of steroids, and Grade 3–4 hematologic toxicity in 28% of patients. Chemotherapy was stopped in 2 patients, delayed in 9 patients and reduced in 4 patients. *Conclusions* Standard RT plus concomitant and adjuvant temozolomide is a feasible treatment for elderly patients with newly diagnosed glioblastoma who present with good prognostic factors.

**Keywords** Glioblastoma · Elderly · Radiotherapy · Temozolomide

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## Introduction

Elderly patients represent an increasing group of patients with glioblastoma, and approximately 22% of all patients with glioblastoma are 70 years of age or older [1, 2]. The reported survival in elderly patients with glioblastoma is poor, especially in those with low Karnofsky performance status (KPS) and impaired neurological status [3, 4].

The possibility of association between age-dependent genetic alterations and different survival in elderly patients with glioblastoma has been suggested. TP53 mutations and CDKN2A/p16 deletion have a negative prognostic effect in older patients, whereas EGFR amplification and LOH 1p have positive prognostic effects [5, 6]. For EGFR amplification and TP53 mutations, the prognostic effects in older patients are opposite to those in younger patients.

However, the significance of such molecular markers is still debated and large studies have not confirmed the impact of these common genetic alterations on survival in patients with glioblastoma [7].

In general, treatment of glioblastoma in the elderly appears to be associated with greater toxicity and reduced efficacy than in younger patients, leading many physicians to choose less aggressive treatment. The majority of elderly patients with glioblastoma are treated with standard or abbreviated courses of radiotherapy (RT) with a median survival of 4–8 months [3, 8–15]. More recently, temozolomide has been proposed as an alternative effective treatment in these patients improving survival and quality of life [16–18].

The recent published randomized European and Canadian trial (EORTC/NCIC) [19] has clearly demonstrated that the addition of temozolomide to RT, followed by 6 monthly cycles of temozolomide in patients <70 years with glioblastoma provides significant survival benefit with minimal additional toxicity. The median survival was 14.6 months with RT plus temozolomide and 12.1 months with RT alone, with a respective two-year survival rate of 27% and 10%, respectively. However, older patients are frequently excluded from randomised studies and it is not clear whether the morbidity associated with an aggressive treatment outweighs the possible survival benefit in this population.

The purpose of this study was to assess the effect of combination of standard RT and chemotherapy on survival in elderly patients with glioblastoma who presented with a good performance status.

## Patients and method

### Patients

Patients aged >70 years with newly diagnosed and histologically confirmed GBM, with a Karnofsky performance status (KPS) $\geq$ 70, good neurological status and who underwent complete/partial surgery were enrolled in this prospective study. All patients were required to have normal hematologic, liver, and renal function before treatment. No patient received previous RT or chemotherapy. Concurrent medications were permitted and included anticonvulsants ($n = 4$), dexamethasone ($n = 6$) and anticoagulants ($n = 2$). Commorbodity was represented by diabetes ($n = 11$), hypertension ($n = 10$) and cardiovascular disease ($n = 8$). If progression occurred, further treatment was at the physician's discretion. All patients provided written informed consent form prior to study participation. The study protocol was approved by the local ethics committees.

### Study design and treatment

All patients received focal RT plus concomitant daily temozolomide, followed by adjuvant temozolomide. RT started within 4 weeks after surgery and consisted of fractionated focal irradiation, at the dose of 60 Gy delivered in 30 fractions of 2 Gy during 6 weeks, with 3 or 4 orthogonal beams. A computed tomography (CT) or a fused image of CT and magnetic resonance imaging (MRI) were used to define the gross target volume (GTV). The planning target volume (PTV) was defined as GTV plus 2–3 cm margin in three dimensions. Conformal RT was carried out using a three-dimensional (3D) planning system and delivered with 6 MV linear accelerator using a multileaf collimator.

Concomitant chemotherapy consisted of temozolomide at the dose of 75 mg/m$^2$, given 7 days per week from the first day of RT. Adjuvant temozolomide was started 4 weeks after the end of RT and delivered for 5 days every 28 days up to 6 cycles. The dose was 150 mg/m$^2$ for the first cycle and was increased to 200 mg/m$^2$ from the second cycle. The dose was reduced to 150 mg/m$^2$ for patients who developed grade 3 or 4 hematologic toxicity, and suspended in patients with disease progression or persistent Grade 3–4 nonhematologic toxicity. Patients received prophylaxis against Pneumocystis Carinii pneumonia (PCP) with sulfamethoxazole-trimethoprim given three times a week (160 mg trimethoprim and 800 mg sulfamethoxazole given Monday, Wednesday, Friday) during concomitant temozolomide and antiemetic prophylaxis during concomitant and adjuvant temozolomide.

Patients were assessed every week during the RT. Subsequently a clinical assessment of neurological status and tolerance to treatment was performed every month. Patients were monitored by blood counts weekly during RT and thereafter before each cycle of adjuvant temozolomide. Safety and tolerability were measured using the national Cancer Institute Common Toxicity Criteria (version 2). Neuroradiographic response criteria as defined by Macdonald et al. [20] were used. Radiological response had to be confirmed at two different MRI evaluations (at least 2 months apart). Tumour progression was defined by an increase in tumour size more than 25% or by the presence of a new lesion on imaging. MRI was repeated before RT, before the first cycle of adjuvant temozolomide and thereafter every 8 weeks.

The primary endpoint was overall survival (OS). Survival was estimated using the Kaplan-Meier method calculated from the time of surgery. Secondary endpoints included progression free survival (PFS) and tolerance to treatment. OS and PFS were stratified by age (>75 years or $\leq$75 years), site of the tumour, residual disease after surgery, commorbidity and KPS at study entry. The longrank

test was used to compare survival according to the prognostic factors. A multivariate Cox proportional hazards regression model was used to test the effect of prognostic factors on OS.

## Results

From January 2001 to April 2005, 32 consecutive patients (18 males and 14 females) were enrolled in this study. The characteristics of patients are shown in Table 1. Median age was 73.6 years (range 70–79). The median KPS before RT was 80 (range 70–100). All patients underwent surgery. The extent of resection was determined from postoperative MRI obtained within 2 weeks before RT ($n = 17$). Gross total resection was achieved in 7 patients, subtotal resection in 17 and partial resection in 8 patients. The median GTV and PTV were 14.8 $cm^3$ (7.6–33.7 $cm^3$) and 165 $cm^3$ (33–260 $cm^3$), respectively. Pathological diagnosis of glioblastoma was confirmed in all patients based on the world Health Organization (WHO) classification.

The median OS was 10.6 months (95% CI 8.6–12.6) (Fig. 1) and the median PFS was 7 months (95% CI 5–9) (Fig. 2). All patients had died at the time of analysis. The 6-month and 12-month survival rates were 91% (95% CI, 79–100%) and 37% (95% CI, 23–50%), respectively. The 6-month and 12-month PFS rates were 56% (95% CI, 38–74%) and 16% (95% CI, 4–28%), respectively. Only two

**Table 1** Individual characteristics of 32 elderly patients with glioblastoma

| Patients | Age | Sex | Tumour site | KPS | Extent of resection | Toxicity | PFS (months) | OS (months) |
|---|---|---|---|---|---|---|---|---|
| 1 | 76 | f | tp | 90 | p | H | 8 | 11 |
| 2 | 76 | m | p | 80 | st | N, H | 7 | 10 |
| 3 | 71 | m | f | 80 | t | No | 12 | 15 |
| 4 | 70 | f | p | 90 | t | No | 14 | 17 |
| 5 | 72 | f | t | 70 | t | N | 8 | 13 |
| 6 | 72 | f | tp | 80 | st | N, H | 8 | 9 |
| 7 | 74 | m | p | 90 | st | No | 13 | 16 |
| 8 | 72 | m | p | 80 | st | N | 4 | 8 |
| 9 | 74 | f | t | 70 | t | H | 4 | 8 |
| 10 | 78 | m | tp | 70 | st | No | 2 | 7 |
| 11 | 72 | m | f | 90 | st | No | 8 | 13 |
| 12 | 70 | m | f | 80 | p | No | 8 | 14 |
| 13 | 70 | f | p | 80 | st | N, H | 6 | 11 |
| 14 | 71 | f | p | 80 | st | No | 8 | 14 |
| 15 | 71 | m | tp | 70 | st | N, H | 4 | 9 |
| 16 | 71 | m | t | 90 | st | No | 18 | 27 |
| 17 | 76 | m | f | 70 | st | N | 4 | 9 |
| 18 | 76 | f | po | 80 | st | N, H | 7 | 11 |
| 19 | 74 | m | p | 70 | p | No | 2 | 4 |
| 20 | 73 | f | f | 90 | t | No | 8 | 13 |
| 21 | 75 | f | t | 90 | st | N | 13 | 17 |
| 22 | 78 | m | tp | 90 | p | No | 4 | 8 |
| 23 | 71 | m | p | 80 | p | N | 4 | 8 |
| 24 | 76 | f | f | 70 | st | No | 4 | 10 |
| 25 | 72 | m | po | 80 | st | No | 10 | 14 |
| 26 | 74 | f | p | 70 | p | N, H | 4 | 10 |
| 27 | 76 | m | tp | 80 | p | No | 4 | 8 |
| 28 | 76 | m | p | 80 | t | N | 6 | 9 |
| 28 | 74 | f | t | 70 | t | No | 3 | 5 |
| 30 | 79 | m | t | 70 | p | No | 2 | 6 |
| 31 | 75 | m | tp | 80 | st | N, H | 10 | 12 |
| 32 | 72 | f | f | 90 | st | No | 16 | 25 |

p, parietal; f, frontal; t, temporal; o, occipital; t, total; st, subtotal; p, partial; N, neurological; H, hematological

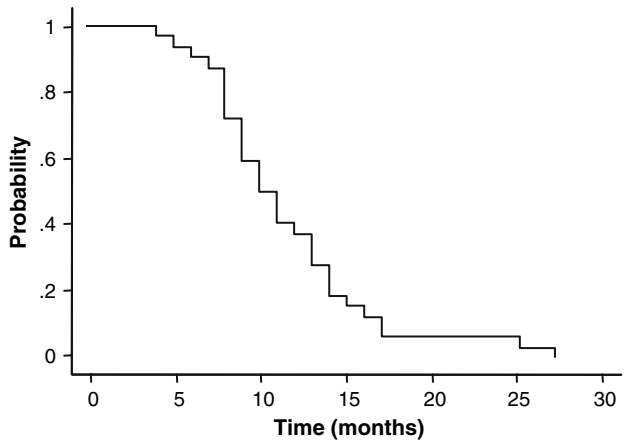


**Fig. 1** Kaplan–Meier analysis of overall survival

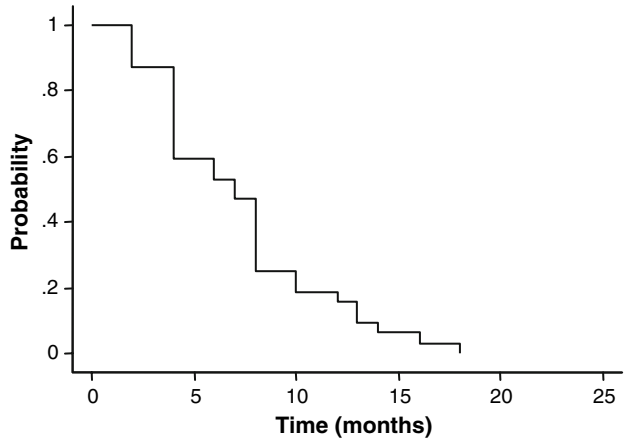


**Fig. 2** Kaplan–Meier analysis of progression free survival

patients survived more than 2 years. Salvage therapies were represented by surgery in 4 patients, re-irradiation in 2 patients and chemotherapy with carmustine in 3 patients.

The differences in survival among subgroups of age ($\leq$75 vs. >75 years, 9.6 months vs. 12.3 months; $P = 0.1$, log rank test), KPS (KPS $\leq$ 70 vs. KPS > 70, 8.1 months vs. 13.4 months; $P = 0.001$, log rank test) and extent of resection (partial resection versus subtotal/total resection, 9.2 months vs. 12.5 months; $P = 0.03$, log rank test) were statistically significant. Age, sex, site of the tumour and presence of commorbidity had no effect on survival. In multivariate Cox proportional hazards regression model KPS was the only significant independent predictive factor (hazard ratios = 0.2, $P = 0.01$). In univariate analysis KPS had an effect on PFS ($P = 0.002$), whereas age and type of surgery were not significant prognostic factors.

A partial response was observed in 7 patients and a minimal response in 6 patients. Responses occurred in 2 patients after concomitant RT and temozolomide, in 3 patients after 2 cycles of temozolomide, in 3 patients after 4 cycles and in 5 patients after 6 cycles.

## Toxicity

All patients were evaluated for toxicity during RT with concomitant temozolomide, the adjuvant-therapy period, and the entire study period. Radiotherapy could not be completed in 2 patients because of severe neurological deterioration (at the dose of 44 Gy in one patient and 48 Gy in another patient). Eleven other patients experienced neurological deterioration during or immediately after RT. Seven patients had Grade 2/3 confusion and/or somnolence, 3 patients Grade 2 memory loss, 2 patients had Grade 2 expressive dysphasia and 1 patient had Grade 2 dizziness. Symptoms were reversible with the use of steroids in 7 patients. MRI showed an increase of peritumoural oedema ($n = 6$) or diffuse leukoencephalopathy ($n = 3$) without evidence of tumour progression. In such patients neurological disturbances were recorded as neurotoxic effects of radiation treatment.

During RT with concomitant temozolomide 2 patients (6%) had Grade 3 hematologic toxic effect (Table 2). Grade 3 neutropenia was observed in one patient and grade 3 thrombocytopenia in another patient. During adjuvant temozolomide therapy, a total of 152 cycles were administered with a median of 5 cycles for patients. Six patients had Grade 3 ($n = 4$) or 4 ($n = 2$) thrombocytopenia and 3 patients had Grade 3 neutropenia. Overall 7 patients (22%) had Grade 3/4 hematologic toxic effect. Chemotherapy was stopped in 2 patients, delayed in 9 patients and reduced in 4 patients. Sulfamethoxazole-trimethoprim prophylaxis was well tolerate, with skin rash and/or pruritus that occurred in 3 patients.

The most common nonhematologic adverse event was a moderate-to-severe fatigue, which occurred in 23 patients. Grade 1/2 nausea and constipation occurred in 11 and 7 patients, respectively. One patient had a deep vein thrombosis after 4 cycles of temozolomide. One patient had a severe lung infection (pneumonia) resolved with medical therapy.

Based on changes on KPS, the patients' ability during the study period (or until tumour progression) improved in 6 patients, remained stable in 20 and worsened in 6 patients.

**Table 2** Hematologic toxicity

| | No of patients (%) | | | |
|---|---|---|---|---|
| | TMZ concomitant | | TMZ adjuvant | |
| Event | Grade 1/2 | Grade 3/4 | Grade 1/2 | Grade 3/4 |
| Trombocytopenia | 3 (9%) | 1 (3%) | 12 (36%) | 6 (18%) |
| Anemia | 1 (3%) | 0 | 4 (12.5%) | 0 |
| Neutropenia | 3 (9%) | 1 (3%) | 5 (16%) | 3 (9%) |

TMZ, temozolomide

## Discussion

The optimal treatment for elderly patients with GBM remains controversial. The majority of patients are treated with standard [14, 21–23] or abbreviated courses of RT [9, 12–15, 21–23] (Table 3).

Villà et al. [18] reported an OS of 8 months in 18 elderly patients > 70 years treated with standard RT at the dose of 60 Gy. Mohan et al. [21] reported a median survival of 7.3 months in 58 patients >70 years treated with standard RT compared to 4.5 months in 19 patients receiving palliative radiation, and similar results have been reported by others [14, 16].

Data from several prospective studies have suggested survival benefit in patients receiving abbreviated courses of RT. In a prospective randomized clinical trial of 100 patients with glioblastoma >60 years, Roa et al. [14] found a similar survival of approximately 6 months amongst patients receiving standard RT or short-course RT (40 Gy in 15 fractions over 3 weeks). More recently, a French randomized trial [15] showed an OS of 29.1 weeks in 39 elderly patients treated with RT (50 Gy in 20 fractions over 4 weeks) as compared with 16.9 weeks in patients who received supportive care alone. Similar survival of 6 months has been reported in elderly patient treated with 30 Gy in six fractions over 2 weeks [9, 10, 13]. In the majority of studies KPS was the strongest predictive factor.

Temozolomide has been recently advocated as an alternative treatment in newly diagnosed elderly patients with glioblastoma [16–18]. Glantz et al. [16] reported a median survival of 6 months in 32 patients treated with temozolomide alone, with a one-year survival rate of 12%. Chinot et al. [17] showed a similar survival of 6.4 months with a one-year survival of 25%. Toxicity was low, with Grade 3–4 thrombocytopenia and neutropenia reported in 6% and 9% of patients.

The current study reports our results in a series of elderly patients presenting with good prognostic factors who received standard RT plus concomitant and adjuvant temozolomide for glioblastoma. The median OS and PFS were 10.6 months and 7 months, respectively. The 6-month and 12-month PFS were 56% and 16%, and respective OS were 91% and 37%.

Our results are consistent with previous other studies on the association of RT and chemotherapy in the treatment of glioblastoma in the elderly [23–26], and compare favorably with studies on the use of RT [3, 14, 21, 22] or chemotherapy [16–18] alone (Table 3). Pierga et al. [25] reported a survival of 13 months in 12 patients receiving RT and carmustine (BCNU) or PVC (procarbazine, lomustine and vincristine) chemotherapy. Gilbert et al. [24] studied a regimen of BCNU and cisplatin, followed by standard RT, in a subgroup of 17 patients ≥65 years and reported a response rate of 76%, with a median survival of 11.9 months.

**Table 3** Main published series on RT and/or chemotherapy for elderly patients with glioblastoma

| Authors | Patients | Age years | RT dose (Gy) | CHT | PFS months | OS months |
|---|---|---|---|---|---|---|
| Bauman et al. [9] | 29 | >65 | 30 | No | NA | 6 |
| Gilbert and Armstrong [24] | 17 | >65 | 60 | BCNU | NA | 11.9 |
| Hoegler and Davey [12] | 25[a] | >70 | 37.5 | No | NA | 8 |
| Mohan et al. [21] | 58 | >70 | 60 | No | NA | 7.3 |
| Villà et al. [22] | 18 | >70 | 60 | No | NA | 8 |
| Pierga et al. [25] | 12[a] | >70 | 45 | PCV/BCNU | NA | 13 |
| | 18[a] | >70 | 45 | No | NA | 6.5 |
| Glantz et al. [16] | 54[a] | >70 | 60 | No | NA | 4.1 (12% at 12 months) |
| | 32[a] | >70 | No | TMZ | NA | 6 (9.3% at 12 months) |
| McAleese et al. [13] | 29 | >70 | 30 | No | NA | 41% at 6 months |
| Brandes et al. [23] | 24 | >65 | 60 | No | 5.3 | 11.2 (31.6% at 12 months) |
| | 32 | >65 | 60 | PCV | 6.9 | 12.7 (56% at 12 months) |
| | 22 | >65 | 60 | TMZ | 10.7 | 14.9 (72.5% at 12 months) |
| Chinot et al. [17] | 32 | >70 | No | TMZ | 5 | 6.4 (25% at 12 months) |
| Roa et al. [14] | 51 | >60 | 60 | No | NA | 5.1 |
| | 49 | >60 | 40 | No | NA | 5.6 |
| Keime-Guiber et al. [15] | 39 | >70 | 50 | No | NA | 7 |
| Present series | 32 | >70 | 60 | TMZ | 6.7 | 10.6 (37% at 12 months) |

[a] Series include anaplastic astrocytomas and glioblastomas BCNU, Carmustine; PVC, procarbazine, lomustine and vincristine; TMZ, temozolomide

However, Grade 3 or 4 toxicity was present in more than 80% of patients. Brandes et al. [23] reported a median OS of 14.9 months in a series of 23 elderly patients >65 years with good prognostic factors treated with standard RT followed by temozolomide and similar results have been reported by others [26].

Despite these results, it is not possible to prove that better OS was the result of the aggressive treatment rather than a reflection of patient selection. In fact most of the patients underwent surgery, had minimal residual disease, KPS > 70 and good neurological status (RTOG RPA class IV). Neverthless, because our results compare favourably with previous published series of RT in patients > 70 years, the reported longer survival suggests that standard RT plus temozolomide may be extended in elderly patients.

Univariate analysis showed that age, KPS and type of surgery were significant prognostic factors. However, at multivariate analysis KPS was the only factor predictive for survival, and this is consistent with previous studies [9, 12, 14, 23, 25]. We agree, according to others [21, 23] that the association of RT and chemotherapy should be systematically considered for all elderly patients who have received surgery and maintain a good performance status. Single prognostic factors such as age or presence of commorbidity should not be the only reason for palliative treatment. In contrast, aggressive treatments do not seem to offer any survival advantage in elderly patients characterized as RTOG RPA class 5–6 [27]. In these patients alternative abbreviated schedules of RT and/or CHT may represent a safer therapeutic approach.

A significant proportion of patients progressed during the six cycles of adjuvant chemotherapy. In the recent EORTC/NCIC trial [19] 06-methylguanine-DNA methyltransferase (MGMT) methylation in glioblastoma was associated with a significant survival benefit when temozolomide was added to RT, whereas those who did not have a methylated MGMT promoter did not have such a benefit [28]. Analysis of MGMT could be considered in future protocols on the use of temozolomide for better stratification of elderly patients who can benefit from aggressive treatments. Similarly, the prognostic effects of potential age-dependent prognostic molecular markers, such as TP53 mutations, EGFR amplification and LOH 1p, could be evaluated in future clinical trials.

Toxicity of standard RT in elderly patients clearly represents a concern in this subgroup of patients, even in those with a good KPS. Roa et al. [14] reported that 26% of patients did not complete standard RT and similar results have been shown by others [4]. In our study two patients (6%) deteriorated neurologically and did not complete the RT. Further eleven patients (34%) have had neurological deterioration during or immediately after RT and required high dose corticosteroids. Toxicity due to standard RT in elderly patients, even manageable in most cases, seems higher than in younger patients [19, 29]. Because an abbreviated course of RT may potentially be associated with a similar survival as for standard RT with reduced toxicity [14], future studies need to define the risk/benefit ratio of different schedules of RT plus temozolomide in this population. PCP prophylaxis was well tolerated with no serious side effects. Although serious complications have been reported, a recent meta-analysis showed a 91% reduction of PCP with severe adverse events occurring in only 3% of adults, and all were reversible [30]. PCP prophylaxis could be considered in elderly patients with GBM who undergo standard RT and temozolomide, especially in those who receive high dose steroids or with lymphopenia.

Severe myelosuppression occurred in 30% of patients, leading to the early discontinuation of chemotherapy in 6% of patients. In the other patients temozolomide cycles were delayed or dose reduced. Our findings confirm that temozolomide is well tolerated and safe also in elderly patients, with no more toxicity compared with younger patients [19, 29, 31].

Quality of life was not addressed specifically in our study. Neverthless, our results show that the majority of responding and stabilized patients maintain or improve their functional status until tumour progression, but KPS is clearly not a measure of quality of life [32].

In conclusion, concomitant chemoradiotherapy followed by adjuvant chemotherapy with temozolomide is a feasible treatment and may prolong the survival of elderly patients with newly diagnosed glioblastoma. Adjuvant temozolomide was well tolerated, however the increased potential neurotoxicity of a full course of RT and concomitant temozolomide in this subgroup of patients requires careful consideration. The impact of different schedules of RT plus concomitant temozolomide on survival and quality of life in the treatment of elderly patients with glioblastoma needs to be addressed in future randomised studies.

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