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REVIEW ARTICLE

Management of elderly patients with glioblastoma-multiforme—a systematic review

¹ASMAA ALMADANI, MSc, BSc, ²SANJAY DIXIT, FRCR, MD, ³CHRIS ROWLAND-HILL, FRCR, ³SHAILENDRA ACHAWAL, FRCS, ³CHITTOOR RAJARAMAN, FRCS, ³GERRY O'REILLY, FRCS, ³ROBIN HIGHLEY, DPhil, FRCPath, ³MASOOD HUSSAIN, FRCS, ³LOUISE BAKER, RGN, BSc, ³LYNNE GILL, BSc, ³HOLLY MORRIS, BSc and ⁴MOHAN HINGORANI, PhD, FRCR, MRCP

¹Faculty of Health Sciences, University of Hull, Hull, UK

²Queen centre of Oncology, Castle Hill hospital, Cottingham, UK

³Department of Neurosurgery, Hull Royal Infirmary, Hull, UK

⁴Leeds Institute of Oncology, Leeds Teaching Hospitals NHS Trust, Leeds, UK

Address correspondence to: Dr Mohan Hingorani

E-mail: mohan.hingorani@nhs.net

ABSTRACT

The management of elderly patients with glioblastoma-multiforme (GBM) remains poorly defined with many experts in the past advocating best supportive care, in view of limited evidence on efficacy of more aggressive treatment protocols. There is randomised evidence (NORDIC and NA-O8 studies) to support the use of surgery followed by adjuvant monotherapy with either radiotherapy (RT) using hypofractionated regimes (e.g. 36 Gy in 6 fractions OR 40 Gy in 15 fractions) or chemotherapy with temozolomide (TMZ) in patients expressing methylation of promoter for O⁶-methylguanine-DNA methyltransferase enzyme. However, the role of combined-modality therapy involving the use of combined RT and TMZ protocols has remained controversial with data from the EORTC (European Organisation for Research and Treatment of Cancer)-NCIC (National Cancer Institute of Canada) studies indicating that patients more than 65 years of age may not benefit significantly from combining standard RT fractionation using 60 Gy in 30 fractions with concurrent and adjuvant TMZ. More recently, randomised data has emerged on combining hypofractionated RT with concurrent and adjuvant TMZ. We provide a comprehensive review of literature with the aim of defining an evidence-based algorithm for management of elderly glioblastoma-multiforme population.

INTRODUCTION

The Age and performance status (PS) represent the two most important prognostic factors in glioblastoma-multiforme (GBM) with superior outcomes reported in younger and good PS patients.^{1–3} An analysis of the Medical Research Council (MRC) database of patients predicted a median survival time of 19 weeks for elderly patients with poor prognostic signs and 28 weeks for elderly patients with good prognostic signs.⁴

The management of elderly patients with GBM has always remained controversial with many experts advocating a purely palliative approach in this group of patients. Halperin et al argued that the considerable time spent by these patients in undergoing treatment may have an adverse effect on their quality of life (QoL) and was not good use of resources in patients with limited prognosis, as it failed to provide extension in terms of acceptable life-years.⁵ However, the above belief is being challenged

with newer evidence demonstrating that active and appropriate intervention may be associated with improved survival.

There is overwhelming evidence that the survival and neurological function outcomes can be maximised through maximal resection in younger patients with malignant glioma. However, many neurosurgeons may avoid aggressive surgical interventions in elderly glioma patients because of probable increased risk of perioperative complications. Similarly, these patients may not be offered adjuvant therapy because of toxicity-related concerns. However, the last two decades has witnessed major advances in surgical and radiation technologies and the development of chemotherapy drugs with convenient administration schedule and superior toxicity profile [e.g. temozolomide (TMZ)], which probably makes it more appropriate for elderly GBM patients to be considered for active intervention compared to in the past. In addition, recent research

has also driven the propaganda for personalised medicine with methylation of promoter for O⁶-methylguanine–DNA methyltransferase (MGMT) emerging as an important predictive marker for response to chemotherapy (TMZ).

In this manuscript, we aim to review the evidence on the emerging therapeutic landscape for elderly patients with GBM and particularly the role of adjuvant therapy [radiotherapy (RT), and chemotherapy].

METHODS AND MATERIALS

We searched the PubMed online database with the following search criteria applied: “glioblastoma” [MeSH terms] AND “elderly” [all fields] AND “humans” [MeSH terms]. The search revealed 269 citations and we identified clinical studies that clearly reported outcome measures (survival and toxicity) in elderly GBM patients following surgery or chemotherapy/RT. We excluded simple observational studies, which reported primarily on patterns of natural disease behaviour/progression without any outcome data. We particularly identified all prospective Phase II and randomised controlled (Phase III) trials, but also included retrospective studies evaluating at least 40 patients especially in domains of therapeutic uncertainty (e.g. combined-modality

therapy, CMT) where there was limited data available from prospective clinical trials.

The results of the PubMed search are schematically illustrated in [Figure 1](#). In summary, we selected 35 studies which had reported outcome after surgery ($n = 4$); adjuvant monotherapy including RT ($n = 7$) or chemotherapy ($n = 4$); CMT including standard RT and TMZ ($n = 12$) or hypofractionated RT and TMZ ($n = 8$). These included 15 prospective [Phase III ($n = 7$); Phase II ($n = 7$); observational ($n = 1$)], 2 pooled retrospective analysis of Phase II studies and another 18 retrospective studies. The studies were reviewed to obtain further details of the study population (demographics, PS), treatment schedules [surgery (biopsy vs resection)], RT (dose-fractionation), chemotherapy (regime, concomitant/adjuvant; number of cycles) and outcome measures (survival and toxicity).

RESULTS

The role of surgery

There are no prospective studies that have evaluated the outcomes following aggressive vs limited resection. In a large retrospective study of 20,705 patients with GBM in the

Figure 1. Schematic illustration of the search strategy and the nature of the studies selected for discussion in the review. RCT, randomized controlled trial; RT, radiotherapy; TMZ, temozolomide.

Surveillance, Epidemiology, and End Results (SEER) database, the frequency of gross total resection (GTR) in patients with GBM decreased in a stepwise manner as a function of patient age [from 36% (18–44 years) to 24% (>75 years) $p < 0.001$]. However, patients who underwent GTR had 2–3-fold increase in overall survival (OS).⁶

D'Amico et al reported on outcomes after surgical resection in 274 elderly patients (>65 years) with GBM. The overall rate of complications after resection was 21.9%, with a rate of neurological complications of 7.7%. However, younger age and improved functional status were associated with a reduced likelihood of complications.⁷

Hofferman et al⁸ reported on surgical outcomes of 124 consecutive patients over 65 years of age. In univariate regression analysis, low Karnofsky performance status (KPS) less than 80 was of negative prognostic value ($p < 0.006$ for KPS ≤ 80), while greater advanced age did not have any impact on survival. Subtotal resection (STR) or GTR was associated with significantly improved OS (median 11.0 and 15.0 months; $p < 0.02$) compared to partial resection or biopsy (both 4.0 months).⁸

Vuorinen and colleagues⁹ reported on a small prospective randomised study of 30 patients in which about 75% patients had malignant glioma. Patients undergoing surgical resection had significantly longer survival time (171 days cf. 85 days; $p = 0.03$) compared to those having biopsy. However, the time to neurological deterioration did not differ significantly between two treatment groups. More recently, a French randomised study is evaluating the impact of surgery on the treatment of supratentorial malignant gliomas in subjects aged 70 and over, and is soon closing to recruitment. The study is expected to recruit approximately 135 participants and will be the largest randomised study to evaluate effects of surgery in malignant gliomas.¹⁰

Almenawer et al performed a meta-analysis study on the role of surgical intervention in 12,607 patients from 34 eligible studies. The researchers noted a significant increase in progression-free survival (PFS) and OS amongst patients, who had undergone either partial or total resection compared to those who had only undergone biopsy. The researchers also noted no change in mortality and morbidity and improvements in KPS in patients undergoing GTR compared to STR. Therefore, the researchers concluded that GTR can result in enhanced recovery of patients' functions, slower tumour progression, and longer periods of survival, whilst still being relatively safe.¹¹ However, another set of researchers argued that the favourable outcomes after aggressive surgical resection may reflect other factors including higher pre-operative KPS and subsequent adjuvant therapy.¹²

Adjuvant radiotherapy

The studies of adjuvant RT are summarised in (Table 1).^{13–19} Keime-Guibert et al reported on a Phase III study in 81 patients (age ≥ 70 years; KPS ≥ 70), who were randomised to best supportive care or adjuvant RT (50.4 Gy/28F – 5 days per week). Patients treated with best supportive care had a median OS of 16.9 weeks compared to 29.1 weeks in the adjuvant RT group [hazard ratio, HR = 0.47 (95% CI 0.29 to 0.76); $p = 0.002$]. There were no severe adverse events related to RT and the QoL and cognitive evaluations over time did not differ significantly between the treatment groups.¹³

Bauman et al reported on prospective small pilot study of 29 patients (>65 years and/or KPS < 50) treated with 30 Gy in 10 fractions to whole brain that demonstrated median OS of 6 months.¹⁴ Mcaleese et al reported on 92 patients with poor-prognosis GBM treated with hypofractionated RT (HRT) using 30 Gy in six fractions (F) and demonstrated median OS of 5.1 months with a 1-year survival rate of 12%, which was associated

Table 1. Summary of studies of adjuvant radiotherapy

Author	Study population	Study design	Survival
Keime-Guibert et al (2007) ¹³ Phase III	Phase III study N = 81 patients (≥ 70 years; KPS ≥ 70)	BSC or adjuvant RT (50.4 Gy/28F)	Median OS of 16.9 weeks (BSC) compared to 29.1 weeks (RT)
Bauman et al (1994) ¹⁴ prospective pilot study	N = 29 (>65 years and/or KPS < 50)	30 Gy in 10 fractions to whole brain	Median OS of 6 months.
McAleese et al (2003) ¹⁵ retrospective	N = 92 patients Poor-prognosis GBM	30 Gy in six fractions (three fractions per week)	Median OS 5.1 months with a 1-year survival rate of 12%
Ford et al (1997) ¹⁶ single-arm Phase II	N = 32 Poor-prognosis GBM	36 Gy in 12 fractions	Median OS 16 weeks
Roa et al (2004) ¹⁷ Phase III	N = 100 (>60 years)	SRT (60 Gy/30 F) cf. HRT (40 Gy/15 F)	Median OS 5.1 months (SRT) group and 5.6 months (HRT) group ($p = 0.57$)
Roa et al (2015) ¹⁸ Phase III	N = 98 (KPS 50–70%; ≥ 65 years)	Arm 1 = 25 Gy/5 F Arm 2 = 40 Gy/15F	Median OS 7.9 months (Arm 1) cf. 6.4 months (Arm 2) $p = 0.98$
Malmström et al (2012) ¹⁹ Phase III NORDIC study	N = 342 (>60 years)	SRT (60 Gy/30 F) cf. HRT (34 Gy/10 F)	In patients > 70 years SRT inferior to HRT; HR = 0.59 (0.37–0.93), $p = 0.02$

BSC, best supportive care; HR, hazard ratio; HRT, hypo-fractionated RT; OS, overall survival; PFS, progression-free survival; SRT, standard radiotherapy.

with an objective stability or an improvement in functional status. The survival was inferior to matched controls treated with conventionally fractionated RT [standard RT (SRT) 60 Gy/in 2 Gy per fraction], but was compensated by the lower intensity and duration of radiation-induced side effects. The authors postulated about probable similar “quality adjusted survival” between the two regimens.¹⁵

Ford et al reported on a small UK prospective series of 32 patients with high-grade glioma and poor prognostic features treated with HRT using a dose of 36 Gy in 12 fractions. 28 patients completed treatment as planned and the median OS for the whole group was 16 weeks, with seven patients surviving for more than 6 months. A matched case-control comparison with data from patients in previous MRC studies showed that these results were similar to conventional fractionation for this group of patients.¹⁶

The effects of HRT using 34 Gy in 10 fractions was compared to SRT in the NORDIC trial and demonstrated superior survival after HRT compared to SRT.¹⁹ In a pivotal Phase III study published by Canadian Group assigned 100 GBM patients aged 60 years or older were randomised to SRT (60 Gy/30 F or HRT (40 Gy/15 F) to the partial brain. The MS was 5.1 months in the SRT group and 5.6 months in the HRT group ($p = 0.57$) that established the non-inferiority of HRT compared to SRT in older patients with GBM.¹⁷ The same group in a subsequent Phase III trial randomised 98 patients (frail = KPS 50 to 70 OR elderly = ≥ 65 years OR both) to two different HRT schedules of Arm 1 = 25 Gy/5F (1 week) or Arm 2 = 40 Gy/15 F (3 weeks). There was no difference in survival outcomes between two schedules with median OS of 7.9 months in Arm 1 and 6.4 months in Arm 2 ($p = 0.988$). Similarly, there was no difference in terms of QoL between both arms at 4 and 8 weeks after treatment.¹⁸

Adjuvant chemotherapy

Perez-Larraya et al reported on Phase II study in 70 patients with poor-prognosis GBM (KPS < 70; age ≥ 70), who were treated with 150–200 mg m⁻² day⁻¹ TMZ for 5 days every 4 weeks until disease progression without any adjuvant RT. The researchers noted 13% incidence of Grade 3 or 4 neutropaenia and 14% incidence of Grade 3 or 4 thrombocytopaenia. The median PFS was 16 weeks and median OS was 25 weeks comparable to outcomes observed after RT alone and better than the 12- to 16-week OS observed with best supportive care. Furthermore, 33% of patients experienced a 10-point or higher improvement in KPS, whilst 26% became capable of self-care and QoL and cognition improved over time before disease progression. In addition, presence of methylated MGMT status was associated with longer PFS (26 vs 11 weeks; $p = 0.03$) and OS (31 vs 19 weeks; $p = 0.03$).²⁰

Malmström et al reported on the pivotal Swedish Phase III NORDIC study in which 342 newly diagnosed GBM patients over the age of 60 were randomised to TMZ at 200 mg m⁻² on days 1–5 of every 28 days for up to six cycles, or HRT at 34 Gy/10 F (2 weeks) or SRT at 60 Gy/30 F. The median OS of patients treated with TMZ or HRT was similar [8.4 months cf. 7.4 months; HR 0.82, 95% CI (0.63–1.06); $p = 0.12$]. In patients

over 70 years, survival was better with TMZ or HRT compared with SRT (TMZ vs SRT: HR = 0.35 [95% CI (0.21–0.56)], $p < 0.0001$ and HRT cf. SRT: HR = 0.59 [95% CI (0.37–0.93)], $p = 0.02$). Furthermore, patients treated with TMZ had superior OS in presence of MGMT methylation (9.7 months cf. 6.8 months HR 0.56 [95% CI (0.34–0.93)], $p = 0.02$), whereas no such differences were observed with HRT.¹⁷

Wick et al reported on the German Phase III NA-O8 trial, which randomised 412 patients (KPS ≥ 60 , age ≥ 65 years) to TMZ at dose of 100 mg m⁻² ($n = 195$) on days 1–7 of 1-week on/1-week off cycles, or SRT ($n = 178$). The trial reported median OS of 8.6 months, with TMZ compared to 9.6 months with RT (HR = 1.09, 95% CI (0.84–1.42), P (non-inferiority) = 0.033). MGMT promoter methylation was associated with longer OS compared to unmethylated tumours (median OS 11.9 months cf. 8.2 months; HR 0.62, [95% CI (0.42–0.91), $p = 0.014$]). Patients treated with TMZ had superior PFS in presence of MGMT methylation, whereas opposite trend was observed with RT.²¹

Yin et al conducted a meta-analysis on the use of RT vs TMZ that included two randomised studies discussed above and further three comparative studies. The study demonstrated a survival benefit in favour of TMZ compared with RT [HR = 0.86, 95% CI (0.74–1.00)]. However, analysis of the NA-O8 and NORDIC studies alone could only demonstrate non-inferiority [HR 0.91, 95% CI (0.66–1.27)]. Patients with MGMT methylation had longer OS and in these patients the use of TMZ was found to be superior compared to RT alone [HR 0.66, 95% CI (0.47–0.93)], whereas the opposite was true for those with unmethylated tumours [HR 1.32, 95% CI (1.00–1.76)]. The authors commented on the caveat of increased Grade 3–4 toxicity haematological toxicity in elderly patients and recommended assessment of MGMT for selecting patients appropriate for TMZ.²²

Combined-modality therapy (CMT)

Standard RT (SRT (60 Gy/30 F)) and TMZ

Most of the evidence on the role of SRT $\pm$ TMZ is from small retrospective studies that is summarised in (Table 2).^{23–34} These studies have demonstrated average median OS ranging between 10 and 12 months with most studies indicating an improvement in survival outcomes with CMT compared to RT alone. In one of the larger retrospective studies including 291 patients more than 65 years, the use of SRT and concurrent TMZ improved median OS of patients with favourable prognostic factors from 12 to 21 months and from 10 to 13 months in patients 65–70 and ≥ 71 years old, respectively ($p < 0.01$).²⁵

Franceschi et al reported on outcomes of 76 patients (>70 years; PS = 0–3) enrolled in the Italian prospective observational population-based (PERNO, Project of Emilia Romagna Region on Neuro-Oncology) study. The median OS in patients treated with SRT + TMZ was 11.6 months [95% CI (8.6–14.6)] compared to 9.3 months [95% CI (8.1–10.6)] in patients treated with RT alone ($p = 0.164$). However, patients with MGMT methylation treated with RT/TMZ had median OS of 17.2 months [95% CI (11.5–22.9), $p = 0.042$].²⁶

Table 2. Summary of studies of SRT (60 Gy in 30 fractions) and TMZ

Author	Study population	Study design	Survival
Balducci <i>et al</i> (2012) ²³ retrospective pooled analysis of three Phase II studies	N = 56 (>65 years)	SRT (60 Gy/30 F) with concurrent and adjuvant TMZ	No increase in acute toxicity 98% completed treatment Median PFS (12 months) and OS (18 months)
Fiorentino <i>et al</i> (2015) ²⁴ retrospective pooled analysis of four Phase II studies	N = 111 (>65 years)	RT (60 (SRT) or stereotactic fractionated RT (69.4 Gy) or IMRT (63 Gy) and concurrent/adjuvant TMZ	Median PFS (10 months) and OS (13 months) Extent of surgery and radiation dose important prognostic factors
Barker <i>et al</i> (2012) ²⁵ retrospective	N = 291 (>65 years)	SRT (60 Gy/30 F) compared with SRT and concomitant TMZ	Median OS 12 months (RT) cf. 21 months (CRT) 65–70 years ($p < 0.01$) MS 10 months (RT) cf. 13 months (CRT) > 70 years ($p < 0.01$) ≥Grade 3 haematological toxicity higher
Franceschi <i>et al</i> (2016) ²⁶ prospective observational	N = 76 (>70 years)	SRT (60 Gy/30 F) compared with SRT and concomitant TMZ	Median OS 11.6 months (CRT) cf. 9.3 months (RT) ($p = 0.16$) MS 17.2 with CRT in MGMT methylated patients ($p = 0.04$)
Behm <i>et al</i> (2013) ²³ retrospective	N = 293 (>65 years)	SRT (60 Gy/30 F) compared with SRT and concomitant TMZ	Median OS 3.6 months (RT) cf. 8.7 months (CRT) > 65 years ($p < 0.001$) Median OS 3.2 months (RT) cf. 9.2 months (CRT) > 75 years ($p < 0.001$)
Brandes (2009) ²⁷ retrospective	N = 58 (>65 years)	SRT (60 Gy/30 F with) with concurrent and adjuvant TMZ (12 cycles)	Median PFS = 9.5 months and OS = 13.7 months MGMT methylation associated with increased survival ($p = 0.05$) Grade 3–4 mental deterioration in 25% Leukoencephalopathy in 10%
Gerstein <i>et al</i> (2010) ²⁸ retrospective	N = 51	SRT (60 Gy/30 F with) with concurrent (all patients) and adjuvant TMZ (10 patients))	Median PFS = 5.5 months and OS = 11.5 months Concomitant chemotherapy interrupted in 16/51 patients
Minniti <i>et al</i> (2008) ²⁹ Phase II	N = 32	SRT (60 Gy/30 F with) with concurrent and adjuvant TMZ (12 cycles)	Median PFS of 7 months and OS of 10.6 months 12 month survival of 37% Grade 3–4 haematological toxicity 15% Neurotoxicity 40%—resolved with steroids
Combs <i>et al</i> (2008) ³⁰ retrospective	N = 43	SRT (60 Gy/30 F with) with concurrent (all) and adjuvant TMZ (N = 5)	Median PFS of 4 months and OS of 11 months 12 month survival of 48% and 2-year survival of 8% RT completed with no delays in 38/43 patients Grade 2 haematological toxicity in four patients with TMZ
Pasqualetti <i>et al</i> (2014) ³¹ retrospective	N = 40 (>65 years)	SRT (60 Gy/30 F with) with concurrent (all) and adjuvant TMZ	Median PFS of 10.6 months and OS of 19.3 months Toxicity similar to that observed in younger patients
Abhinav <i>et al</i> (2013) ³² retrospective	N = 59 (>65 years)	GTR (N = 25), STR (N = 8), biopsy (N = 26), CRT (N = 22) and RT (N = 20).	Median OS 316 days (CRT) cf. 143 days (RT) ($p = 0.011$) MGMT did not correlate with survival Median OS with unmethylated MGMT was 308 days cf. 167 days in methylated group
Niyazi <i>et al</i> (2012) ³³ retrospective	N=43	SRT (60 Gy/30 F) compared with SRT and concomitant TMZ	Median OS RT = 314 days cf. CRT = 192 days $p = 0.106$ Significantly worse survival with CRT in patients with KPS < 70

CRT, chemoradiotherapy; GTR, gross total resection; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; SRT, standard radiotherapy; STR, subtotal resection; TMZ, temozolomide.

Minniti *et al* reported on a small Phase II prospective study of 32 patients (age ≥ 70 years; KPS ≥ 70) and surgery followed by SRT with concomitant and adjuvant TMZ. The study reported median OS of 10.6 months and the median PFS was 7 months. In multivariate analysis, KPS was the only significant independent predictive factor of survival ($p = 0.01$). The adverse effects frequently observed included neurotoxicity in 40% of cases

which resolved in most cases with the use of steroids, and Grade 3–4 haematologic toxicity in 28% of patients.²⁹

In a pooled analysis of 4 Phase II studies including 111 patients > 65 years of age with no significant comorbidity and KPS > 70 treatment with RT [SRT (60 Gy) or stereotactic fractionated RT (69.4 Gy) or IMRT (63 Gy)] and concurrent/adjuvant TMZ the

Table 3. Summary of studies of HRT and TMZ

Author	Study population	Study design	Survival
Arvold et al (2015) retrospective ³⁵	N = 135 (>65 years)	HRT (40 Gy/15 F) + concurrent TMZ cf. SRT (60 Gy/30 F) + concurrent TMZ cf. SRT alone (60 Gy/30 F)	No difference in survival outcomes of SRT + TMZ and HRT + TMZ [HR = HR: 1.10, 95% CI (0.50–2.4), $p = 0.82$] SRT alone inferior to concurrent TMZ regimes [1.72; 95% CI (1.06–2.79); $p = 0.03$]
Gzell et al (2014) retrospective ³⁶	N = 69 patients (65–75 years)	SRT (60 Gy/30 F) cf. HRT (40 Gy/15 F) 70% received TMZ ($n = 48$)	Median OS 15 months (SRT) cf. 9 months (HRT) ($p < 0.0001$) Median OS 13 months (TMZ) cf. 7 months (no TMZ) ($p < 0.0001$) Median OS 15 months (60 Gy/30 F + TMZ) cf. 11 months (HRT + TMZ) (not significant)
Minniti et al (2009) Phase II ³⁷	N = 43	HRT (30 Gy/6 F over 2 weeks) followed by adjuvant TMZ (12 cycles)	Median PFS 6.3 months and OS 9.3 months 12-month survival rate 35% Grade 3–4 haematological toxicity 28% with TMZ
Minniti et al (2012) Phase II ³⁸	N = 71	HRT (40 Gy/15 F) with concurrent TMZ followed by adjuvant TMZ (12 cycles)	Median OS of 12.4 months and 2-year survival of 20% Grade 3–4 toxicity 22% Grade 3–4 haematological toxicity 15%
Minniti et al (2015) retrospective ³⁹	N = 243	SRT (60 Gy/30 F) cf. HRT (40 Gy/15 F) combined with concurrent and adjuvant TMZ	Median OS and PFS 12 months and 5.6 months in SRT-TMZ group and Median OS and PFS of 12.5 months and 6.7 months in HRT-TMZ group SRT-TMZ associated with higher Grade 2 and 3 neurologic toxicity ($p = 0.01$), lowering of KPS scores ($p = 0.01$), and higher dosing of corticosteroid cf. HRT-TMZ
Cao (2012) retrospective ⁴⁰	N = 112 (>65 years)	HRT cf. HRT + concurrent and adjuvant TMZ	Median OS of 9.3 months in HRT + TMZ arm cf. 6.9 months in HRT arm Median OS of 13.3 months in patients receiving HRT followed by salvage TMZ
Muni et al (2010) Phase II ⁴¹	N = 45 (>70 years; ≤ 70 years with KPS < 70)	HRT (30 Gy/6F) cf. HRT + adjuvant TMZ ($n = 22$) (12 cycles)	Median OS of 7.3 months (HRT) cf. 9.4 months (HRT + TMZ) ($p = 0.003$) Median PFS of 4.4 months (HRT) cf. 5.5 months (HRT + TMZ) ($p = 0.01$)
Perry et al (2016) Phase III ⁴²	562 patients (ECOG 0–2; >65 years)	HRT ($n = 281$) cf. HRT + concurrent and adjuvant TMZ ($n = 281$) (12 cycles)	Median OS 9.3 months (HRT + TMZ) cf. 7.6 months (HRT) ($p < 0.0001$) Methylated MGMT = Median OS of 13.5 (HRT + TMZ months cf. 7.7 months (HRT) ($p < 0.0001$) Unmethylated MGMT = Median OS of 10 months cf. 7.9 months ($p = 0.05$)
Chang Halpheny et al (2015) retrospective ⁴³	N = 129 (>65 years)	HRT (35 Gy) + concurrent TMZ cf. SRT (60 Gy/30 F) + concurrent TMZ	Median OS 13 months SRT + TMZ cf. 5.4 months in HRT + TMZ group (HR on multivariate analysis = 0.421, $p = 0.0001$) MGMT methylation strong prognostic factor in the combined SRT group.

CRT, chemoradiotherapy; HR, hazard ratio; HRT, hypofractionated therapy; OS, overall survival; PFS, progression-free survival; SRT, standard radiotherapy; TMZ, Temozolomide.

CMT was well-tolerated with compliance of 96.4% with median PFS and OS of 10 and 13 months, respectively.²⁴

Hypofractionated RT (HRT) and TMZ

The comparative efficacy of HRT compared to SRT in elderly poor-prognosis patients with GBM prompted the exploration of combining HRT with TMZ. These studies are summarised in Table 3.^{35–44}

HRT followed by adjuvant TMZ

Minniti et al reported on a prospective Phase II study in 43 patients (≥ 70 years; KPS > 60) treated with HRT (30 Gy/6F over 2 weeks) followed by up to 12 cycles of adjuvant TMZ. The median OS was 9.3 months and the median PFS was 6.3 months. The 6- and 12-month survival rates were 86 and 35%, respectively. Muni et al reported on another randomised Phase II study

including 45 patients with GBM (≥ 70 years; 50–70 years but with KPS ≤ 70), who were randomised to HRT (30 Gy/6F) or HRT and adjuvant TMZ. The median OS was 7.3 months in the HRT group compared to 9.4 months in the HRT + TMZ group ($p = 0.003$). In both above studies, KPS was the only significant independent predictor of survival. Neurological deterioration occurred during or after RT in approximately 20% of patients and Grade 3–4 haematologic toxicity occurred in approximately 30% of patients during the adjuvant chemotherapy. The treatment had no negative effect on QoL, apart from fatigue scales that worsened over time.^{37,41}

HRT combined with concurrent and adjuvant TMZ

Minniti et al reported on Phase II study of 71 elderly patients with GBM (KPS ≥ 60 ; ≥ 70 years) treated with HRT (40 Gy/15

F) with concomitant and adjuvant (12 cycles) TMZ. The median OS was 12.4 months, and the 1-year and 2-year OS rates were 58 and 20%, respectively. All patients completed the planned programme of RT. Grade 3 or 4 adverse events occurred in 16 patients (22%). Grade 3 and 4 neutropaenia and/or thrombocytopaenia occurred in 10 patients (15%), leading to the interruption of treatment in 6 patients (8%). Non-haematologic Grade 3 toxicity was rare, and included fatigue in 4 patients and cognitive disability in one patient.³⁸

More recently, a global multicentre Phase III study of HRT (40 Gy/15 F) with or without concurrent/adjuvant TMZ in 562 patients (≥ 65 years; ECOG PS-0–2) reported the preliminary results at the 2016 Annual ASCO meeting. The use of HRT + TMZ significantly improved OS over RT alone (median 9.3 vs 7.6 months, HR 0.67, [95% CI (0.56–0.80)], $p < 0.0001$). In MGMT-methylated patients ($n = 165$), OS for HRT + TMZ compared to RT was 13.5 and 7.7 months, respectively [HR: 0.53 (95% CI (0.38–0.73), $p = 0.0001$]. In MGMT-unmethylated patients ($n = 189$) OS for RT + TMZ vs RT was 10.0 months compared to 7.9 months, respectively [HR 0.75 {95% CI (0.56–1.01), $p = 0.055$ }. The QoL was similar in both groups in respect of functional domains although incidence of gastrointestinal toxicity was higher in the combined arm.^{42,44}

HRT + TMZ compared to SRT + TMZ

There are no randomised studies that have compared directly HRT + TMZ with SRT + TMZ.

Minniti et al reported on large retrospective study in 243 (age ≥ 65 years; KPS ≥ 60) patients treated with either SRT [60 Gy/30 F ($n = 127$)] or HRT [40 Gy/15 F ($n = 116$)] combined with concomitant and adjuvant TMZ. The median OS was similar in both groups [12 months (SRT + TMZ) cf. 12.5 months (HRT + TMZ)]. The MGMT methylation was the most favourable prognostic factor ($p = 0.0001$). However, SRT + TMZ therapy was associated with a significant rise in Grade 2 and 3 neurologic toxicity ($p = 0.01$), lowering of KPS scores ($p = 0.01$), and higher posttreatment dosing of corticosteroid ($p = 0.02$).³⁹

Arvold et al (2015) reported on another retrospective analysis of HRT [40 Gy/15 F ($n = 34$)] + TMZ compared to SRT [(60 Gy/30 F ($n = 57$)] + TMZ. Patients receiving HRT were significantly older (median: 79 vs 69 years of age; $p < 0.001$) and had worse baseline PS ($p < 0.001$) than those receiving SRT. Despite differences in baseline characteristics, the median OS was similar in both groups [HR: 1.10, {95% CI (0.50–2.4)}, $p = 0.82$].³⁵

In contrast, at least two studies have reported inferior outcomes in patients receiving HRT and TMZ compared to SRT + TMZ. Gzell et al reported on retrospective study of 109 patients with GBM (63% 65–75, and 24% > 75) who were treated with HRT (40 Gy/15 F) or SRT (60 Gy/30 F). The median OS of total group was 12 months with 12% surviving beyond 2 years. In the 69 patients aged 65–75, longer survival was associated with the use of SRT 60 Gy (15 vs 9 months, $p < 0.0001$), and use of TMZ (13 vs 7 months, $p < 0.0001$).³⁶

Chang Halpheny et al reported on retrospective study evaluating the outcomes after HRT (median dose = 35 Gy) and concurrent TMZ ($n = 29$) compared to SRT ($n = 100$) and concurrent TMZ in elderly GBM patients aged more than 65 years of age. The median OS was 13 months in combined SRT + TMZ group compared to 5.4 months in HRT + TMZ group. (HR on multivariate analysis = 0.421, $p = 0.0001$) with MGMT methylation strong prognostic factor in the combined SRT group. However, patients treated with HRT had significantly worse baseline prognostic variables that may have explained the poorer outcomes observed in this group.⁴³

DISCUSSION

Many elderly patients with GBM are managed with best supportive care because of general perception of poor outcomes with conventional treatment modalities. In a SEER database retrospective analysis of 2836 elderly GBM patients (> 70 years), 14% did not undergo any treatment and 22% underwent surgery but no subsequent adjuvant treatment, and 18% had RT alone.⁴⁵ Indeed, these patients have been historically excluded from clinical trials. Furthermore, the definition of “elderly GBM patient remains poorly defined and it remains unclear on whether this should be restricted to patients more than 70 years or should include patients in the 65 or 70 years age subgroup. The management of elderly GBM patients has been previously reviewed.⁴⁶ Previous studies, albeit retrospective, have demonstrated that age should not be sole determinant for precluding aggressive surgical resection and even elderly patients undergoing GTR and STR may experience superior survival compared to partial resection or biopsy with an acceptable risk of postoperative complications. Moreover, further evidence points to the importance of multimodality treatment and administration of appropriate adjuvant therapy following surgery. In a large retrospective study of 2836 elderly GBM patients (≥ 70 years) from SEER database, the median survival for patients who underwent surgery and RT was 8 months compared to 3 and 4 months treated with surgery or RT alone, respectively. Those who received neither surgery nor RT had a median survival of 2 months ($p < 0.001$). The study demonstrated that adjuvant RT significantly improved cancer-specific survival compared to surgery alone [HR = 0.43 95% CI (0.38–0.49)].⁴⁵

In another retrospective cohort of 265 patients, more than 70 years from French Brain Tumour Data Base patients undergoing biopsy followed by RT had median OS of 149 days compared to 269 days in those receiving RT after surgical resection. Furthermore, patients having resection followed by adjuvant chemoradiotherapy (CRT) median OS of 372 days. The authors argued that elderly patients are undertreated and surgery and adjuvant CRT should be considered for good PS patients.⁴⁷

The MRC BR2 study demonstrated superiority of 60 Gy/30 F over 45 Gy/20 F with significant prolongation of median survival from 9 to 12 months ($p = 0.007$). The above trial established the role of adjuvant RT using 60 Gy/30 F as standard of care (standard RT) in patients after surgical intervention. However, the outcome of elderly and poor PS patients treated with standard radiation regimes extending over 5–6 weeks remained poor.⁴⁸

A multivariate analysis of three randomized RTOG (Radiation Therapy Oncology group) protocols using protracted radiation therapy and chemotherapy in GBM showed that patients over 60 years of age had a median survival of 24 weeks.⁴⁹

Subsequent studies have demonstrated non-inferiority of shorter HRT protocols (compared to SRT) and offer distinct advantage in terms of shorter duration of treatment with no apparent increase in toxicity.¹⁷ The HRT regime of 36 Gy in 6 fractions or 40 Gy in 15 fractions are most commonly employed, but the alternative regime of 25 Gy in five fractions is an attractive option based on the results from the recent Canadian Phase III study, particularly in terms of treatment duration and completion in less than a week.¹⁸

The publication of the pivotal European Organisation for Research and Treatment of Cancer (EORTC) Phase III randomised trial in 2005 established the role of adjuvant SRT (60 Gy/30 F) combined with concurrent and adjuvant TMZ as standard of care in newly diagnosed GBM. However, the trial excluded patients more than 70 years of age but 170 of the 573 patients (30%) were aged 61–70 years. For this older subset of patients, median OS using the combined-modality approach compared to radiation therapy alone was similar (median 10.9 vs 11.8 months).⁵⁰ In subsequent update with mature FU the benefits of adjuvant TMZ with RT lasted throughout 5 years of follow up [HR = 0.6, 95% CI (0.5–0.7); $p < 0.001$] and the benefit from CMT was also maintained in 61–70-year age Group.⁵¹ However, a subgroup analysis noted a trend of decreasing benefit from the addition of TMZ with increasing age, such that for age 65–71, the hazard ratio of 0.8 did not reach statistical significance ($p = 0.340$).

Yin et al (2013) reported on a meta-analysis of published studies to validate the effectiveness of using combined-modality approach in elderly GBM patients. No eligible randomized trials were identified and 16 non-randomised studies (5 prospective and 11 retrospective) were analysed. Combined approach using RT and TMZ was shown to reduce the risk of death and progression in elderly GBM patients compared with RT alone ([HR = 0.59, 95% CI (0.48–0.72)].⁵²

More recently, the Canadian Phase III study established the role of CMT using HRT + TMZ in elderly GBM patients (≥ 65 years) which was superior to HRT alone.^{12,49} This is the first randomised study demonstrating efficacy of adjuvant CMT in elderly GBM patients. In our institution (Hull Royal Infirmary), all patients more than 70 years of age with good PS (0–1) are treated with HRT (40 Gy in 15 fractions) with concurrent and adjuvant TMZ. Our personal approach for patients 65–70 years and good PS (0–1) would include SRT (60 in 30 fractions) with concurrent and adjuvant TMZ, but this remains controversial. Many oncologists may favour the hypofractionated protocol in context of the results from the Canadian study and a subgroup analysis from the EORTC study failing to demonstrate survival benefit of standard CRT in patients more than 65 years of age. There has been no randomised comparison of HRT + TMZ and SRT + TMZ, but at least one retrospective study demonstrated that in patients 65–75 years longer survival was associated with

the use of SRT (15 vs 9 months, $p < 0.0001$), and TMZ (13 vs 7 months, $p < 0.0001$).³⁶ Similarly, in the Italian observational population-based prospective study (PERNO) the median OS of patient treated with SRT + TMZ in presence of MGMT methylation was nearly 18 months.²⁶ However, other retrospective studies have demonstrated comparable efficacy of the two regimes with no obvious benefit of using prolonged fractionation in patients more than 70 years of age.^{35,39} In view of the conflicting data, it is difficult to make definite recommendations in the 65–70 age group and there is likely to remain variation in clinical practice with some oncologists preferring SRT + TMZ over HRT protocol, particularly, in patients with MGMT methylation. We also doubt that there will be a randomised study exploring the efficacy and tolerability of SRT + TMZ compared to HRT + TMZ specifically in the 65–70 year subgroup and both protocols would be appropriate therapeutic options in this group of patients.

The importance of PS in selecting patients for CMT was highlighted in retrospective study of 43 GBM patients (≥ 70 years), in which patients treated with SRT and concurrent TMZ demonstrated trend towards inferior survival of 192 days compared with 314 days with RT alone. However, the difference was only significant in those with KPS 70 or less ($p = 0.027$). The authors concluded that CMT may only be a possible treatment option for elderly GBM patients with good prognostic factors.³³ The significance of PS as being the single-most important factor for appropriate selection of patients for CMT has also been highlighted by other studies.^{37,41}

The importance of MGMT methylation as predictive marker for selecting patients for adjuvant chemotherapy with TMZ was demonstrated by the NA-O8 and the NORDIC studies in which use of TMZ was superior to RT in patients with MGMT methylation with converse being true for unmethylated patients.^{17,21} However, despite the prognostic significance of MGMT methylation it cannot be used as a sole factor in selecting patients for CMT as more recent evidence indicates that patients with unmethylated MGMT may still benefit from combined-modality treatment.^{32,44}

The role of second-line therapy in elderly GBM patients is poorly defined with paucity of data or prospective evidence to guide any definite therapeutic recommendations. However, based on the emerging evidence that age should not be the only determinant for guiding therapeutic decisions, it would be reasonable to assume that elderly GBM patients with good PS should be considered for appropriate second-line options but with careful discussions surrounding the caveats of toxicity and potential adverse effects on QoL. The probable second-line options would include nitrosourea-based chemotherapy (single agent lomustine) or anti-angiogenics (bevacizumab) with appropriate dose-modification considering the age and other cofactors (e.g. comorbidities etc).

It is important that further research continues to explore other therapeutic opportunities and promotes development of protocols with potential for reduced toxicity. Therefore, future design of clinical trials should incorporate specific primary end points to assess the tolerance and side-effect profile of various

Figure 2. Evolving treatment algorithm for management of elderly patients with GBM. HRT, hypofractionated RT; KPS, Karnofsky performance status; RT, radiotherapy; TMZ, temozolomide; SRT, standard radiotherapy.

therapeutic modalities and potential effects on overall QoL. The possible areas of research for the future include integration of RT with other radiation response modulators including DNA repair inhibitors and other novel radiosensitising agents. In the UK, the Phase I PARADIGM (BR32) study is evaluating the role of poly-ADP ribose polymerase inhibitor olaparib in conjunction with RT.⁵³ In another UK randomised study (completed recruitment), elderly GBM patients (>70 years) were randomised to an experimental arm of hydroxychloroquine + RT compared to RT alone.⁵⁴ The results from these studies are eagerly awaited and may pave new avenues for managing elderly GBM patients. It is possible that elderly GBM is characterised by a distinct molecular signature which remains elusive and has not been decoded. Indeed, a clearer understanding of the molecular and genetic landscape of elderly GBM may open up possibilities for personalised medicine and identification of other novel therapies in GBM.⁵⁵

CONCLUSION

The management of elderly patients with GBM has significantly evolved with emergence of several new pieces of evidence to indicate that these patients should be considered for active intervention including surgery and adjuvant oncological therapy. The evolving treatment algorithm for elderly GBM patients is summarised in Figure 2. There appears to be continuous linear increase in survival after combination of different modalities with best outcomes observed in patients undergoing aggressive surgical resection followed by adjuvant CRT combined with TMZ. However, appropriate selection is of paramount importance with PS being the most important prognostic factor in selecting patients appropriate for active treatment including surgery and combined-modality treatment. Molecular stratification and analysis of MGMT methylation may help to identify patients who may particularly benefit from CMT and TMZ.

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