

# Narrative review of palliative hypofractionated radiotherapy for high grade glioma

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**Abstract:** High grade gliomas (HGG) include World Health Organization (WHO) grade III anaplastic astrocytoma (AA) and WHO grade IV glioblastoma (GBM). As genomic alterations are prognostic, even WHO grade II, IDH-wildtype gliomas may be considered as HGG. Current management of HGG include best supportive care (BSC), surgery, radiation therapy (RT), chemotherapy, and a combination. Elderly patients (defined here as age  $\geq 65$ ) with GBM have significantly worse survival compared to younger patients. Similarly, patients with poor performance status [defined as Karnofsky performance status (KPS)  $< 60$  or ECOG performance status (PS)  $> 2$ ], regardless of age have worse outcomes. The standard of care for treatment of HGG involves surgery and chemoradiation. However, the optimal treatment in terms of efficacy, safety and maintaining quality of life (QoL), remains a matter of debate in the elderly and/or poor performing patients due to their worse prognosis. Less aggressive interventions are usually reserved for these patients despite surgery providing a survival and neurologic benefit. Improved survival has been noted in elderly patients treated with RT in comparison with those receiving best supportive care (BSC) alone, with similar survival for patients undergoing standard RT (60 Gy/30 fractions) and hypofractionated RT (25–40 Gy in 5–15 daily fractions). An alkylating agent, temozolomide (TMZ), represents a safe and effective option in select patients with promoter methylation of O6-methylguanine-DNA-methyltransferase (MGMT) gene. A recent phase III randomized trial for GBM patients (age  $\geq 65$  years, ECOG PS 0–2) demonstrated a significant improvement in progression-free survival (PFS) and overall survival (OS) with hypofractionated RT (40 Gy/15 fractions) with concurrent and adjuvant TMZ vs. RT alone, without adversely impacting either QoL or functional status. Despite chemoradiation becoming the recommended treatment in GBM patients who are elderly but fit, several questions remain unanswered. This includes the survival impact of chemoradiation in patients with severe comorbidities or with ECOG PS  $> 2$  or a combination of poor prognostic features such as male gender, poor neurocognition, biopsy only and lack of MGMT methylation. Personalized management of patients with HGG is warranted in the modern era as we attempt to balance the benefit of efficacious treatment with potential toxicity while appreciating the many nuances associated with multiple prognostic factors on anticipated survival. Here, we aim to review the palliative management options available for HGG patients with an emphasis on the role of RT.

**Keywords:** Glioma; glioblastoma (GBM); palliation; radiotherapy; hypofractionation

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## Introduction

Gliomas constitute almost 80% of all primary malignant brain tumors with an incidence of 3.2/100,000 for glioblastoma (GBM) in the United States (1,2). Median age at diagnosis of GBM is 64 (3). The incidence and mortality rate of GBM increases with advanced age (4,5). Ladomersky reported a 3.4 times higher incidence of GBM and 7 times higher mortality rate among individuals age  $\geq 65$  vs. age  $< 65$  respectively (6). Furthermore, as the collective world population survives longer, the proportion of elderly GBM patients is predicted to increase as well. These observations highlight the current and future public health needs in managing elderly GBM patients (7).

Approximately, 54% of gliomas are GBMs (8,9) with IDH-mutant GBMs making up about  $< 10\%$  of all GBMs (2,10). IDH-mutant GBMs occur in younger adults (mean age 45 years) compared with IDH-wild type (wt) GBMs (mean age  $> 55$  years), and have a more favorable prognosis, with a median survival  $\sim 2\times$  longer than that of IDH-wildtype tumors (11,12). In a study that reclassified 1,210 gliomas samples according to updated 2016 WHO CNS diagnostic criteria, GBM with IDH-wt was associated with the highest median age at diagnosis (median age 50) (13). Similarly, 65% of AA are IDH-mutant and occur more often in younger patients ages 30–50 (14,15).

The classification of gliomas is an actively evolving field with much of the historical outcome data based on conventional histopathological features. However, recent developments of molecular and genetic factors have allowed us to create subsets that show more accurate and meaningful correlation between their perceived and actual outcomes. *Table 1* depicts the range of gliomas categorized as HGG.

The median survival for GBM is 15 months (16) and for AA is 36 months (17). Age and performance status (PS) as measured by WHO PS or Karnofsky performance status (KPS) can significantly impact survival and are illustrative of the two most important prognostic factors in GBM (18–21). This has been shown by large retrospective studies reporting a median survival of 6 months for GBM patients (age  $> 65$ ) versus 14.6 months for patients in the randomized controlled trial by Stupp (median age 56 years old) (22–26). A multivariate analysis of three randomized Radiation Therapy Oncology group (RTOG) protocols using standard radiation therapy (RT) and chemotherapy for GBM showed reported a median survival of 24 weeks for patients greater than 60 years of age (27). Other factors associated with poor prognosis include differences in the GBM biology

such as higher incidence of IDH-wt (11,28,29), age-related variations in the central nervous system (CNS) that augment gliomagenesis and proliferation (30), male gender, lack of MGMT methylation, biopsy only and poor neurocognition (31).

While the current standard of care for younger, good performing patients includes surgical resection, concurrent chemoradiation with temozolomide (TMZ) and adjuvant TMZ for GBMs or the recently suggested regimen of adjuvant TMZ/lomustine for methylated GBMs (26,32,33), the maximally-effective treatment of geriatric or poor PS GBM patients had not been clearly defined. This lack of data is a direct of consequence of traditional exclusion of patients over the age of 70 years from clinical trials, due to their presumed decreased prospect of a sustained treatment response and/or a good outcome. Additionally, all the patients enrolled in the Stupp and Herrlinger trials had a PS  $\leq 2$  (corresponding to KPS  $\geq 60$ ) and KPS  $\geq 70$  respectively. Of note, among patients treated in the Stupp trial, older patients (65–70 years) appeared to derive less benefit with chemoradiation compared to younger patients (HR = 0.78; P = 0.29) (34).

Complicating this aforementioned lack of data are factors such as higher frequency of age-related-polypharmacy, medical co-morbidities and an increased likelihood of treatment-related toxicity, that results in controversy regarding optimal treatment paradigm for elderly and/or poor PS GBM patients (26,35,36). These patients are less likely to receive aggressive surgery, radiation, chemotherapy, or combined modality treatment. A probable increased risk of perioperative complications, radiation induced fatigue and cognitive decline and chemotherapy induced hematologic effects can culminate in hesitation to employ those modalities. The social situation of these patients must also be considered. Usually, caregivers of elderly patients who embrace the physical, financial, temporal, emotional and social expenses associated with scheduling, billing, transporting and assisting a loved one are often elderly themselves (37,38). This can potentially exacerbate any medical, economic, and psychosocial risks for both the patient and the caregiver, and underscores need for constant communication and support between medical providers and the patients during the entire treatment journey. This necessitates subsequent thoughtful use of treatment options to improve survival without adding excessive toxicities or adversely impacting QoL.

Herein, we aim to review the evolution and use of upfront hypofractionated radiation for patients with poor prognosis

**Table 1** Entities included in high grade gliomas (HGG) (Louis 2016, Brat 2018, Bale 2019)

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High grade gliomas (HGG)
WHO grade II, IDH-wt
WHO grade III, IDH-wt or IDH-mutant*
WHO grade IV, IDH-wt or IDH-mutant
IDH-wt with EGFR amp**
IDH-wt with +7/-10***
IDH-wt with TERT mutation****
IDH-wt with H3 K27M-mutant *****

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\*Prognosis better for IDH-mutant compared with IDH-wt, \*\*epidermal growth factor receptor (EGFR) amplification, \*\*\*chromosome 7 gain/chromosome 10 loss, \*\*\*\*telomerase reverse transcriptase (TERT) promotor mutation, \*\*\*\*\*diffuse midline glioma.

(Table 2) that were historically managed with BSC. One can argue that any conventional treatment for GBM is palliative. However, for simplicity, we are defining “palliative” as any regimen which is more contracted than the conventional standard radiation regimen. Detailed role of surgical treatments, systemic options and tumor treating fields are out of the scope of this review but will be briefly described to cover the available treatment options for patients with poor prognosis. The last two decades has been marked with accelerated development in surgery and radiation techniques as well as radiation fractionation schedules and chemotherapy with enhanced toxicity profile, convenient scheduling and straightforward administration such as TMZ, making these more appropriate for delivery in the palliative setting for GBM patients. Since there have been no trials specifically looking at HGGs other than GBMs, we will be looking at the available data for palliative treatment of GBM and use it to extrapolate to other non-GBM HGGs. We present the following article in accordance with the NARRATIVE REVIEW reporting checklist (available at <http://dx.doi.org/10.21037/apm-20-1246>).

## Methods

MEDLINE and EMBASE were searched using the terms “glioblastoma” or “gbm” or “high grade glioma” and “palliative” or “hypofractionation” or “hypofractionated radiotherapy” from 1975 through June 2020. The references of retrieved articles were searched. Relevant book chapters

**Table 2** Factors associated with poor prognosis in HGG patients

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Poor prognostic signs for high grade glioma (HGG) patients

- Increasing age (defined here as  $\geq 65$ )
  - Poor performance status (KPS <60, ECOG PS >2)
  - Biopsy only
  - Male gender
  - Absence of MGMT methylation
  - IDH-wt
  - Poor neurocognition
  - Lack of radiation and/or chemotherapy
  - Recurrent high grade glioma
- 

KPS, Karnofsky performance status; PS, performance status; MGMT, O6-methylguanine-DNA-methyltransferase.

were reviewed. Websites of various oncologic societies were hand-searched for guidelines. Any papers including only pediatric gliomas or low-grade gliomas were excluded.

## Discussion

### Role of surgery

The role of surgery in the case of palliative treatment of HGG remains controversial. Ethical concerns have precluded any prospective studies evaluating the consequences of aggressive versus limited resection. In a Surveillance, Epidemiology, and End Results (SEER) database study of 20,705 GBM patients, the frequency of gross total resection (GTR) decreased as function of age [36% (18–44 years) vs. 24% (>75 years),  $P < 0.001$ ]. Nevertheless, a 2–3-fold increase in overall survival (OS) was associated with GTR (39). Similarly, an Austrian study found a significantly improved OS associated with subtotal resection (STR) or GTR (median 11.0 and 15.0 months respectively) compared with partial resection or biopsy (median 4.0 months each) (40).

A large meta-analysis of 34 studies involving 12,607 older patients showed significant improvement in progression free survival (PFS) and OS associated with either STR or GTR versus a biopsy only approach. GTR was significantly superior to STR in terms of OS, PFS, improvement in KPS and no changes in mortality or morbidity (41). However, this improvement may demonstrate the heterogeneity of the elderly population and can be driven by other

factors such as higher pre-operative PS and receipt of adjuvant therapy (42). Vuorinen *et al.* reported on a small randomized prospective study of 30 patients, three-fourths of which had malignant glioma. They reported significantly longer survival for patients undergoing surgery compared with a biopsy (171 *vs.* 85 days;  $P=0.03$ ) with no significant differences in neurologic decline (43). D'Amico *et al.* showed an overall rate of complications of 22%, with a rate of neurological complications of 8% after surgical resection in 274 GBM patients (>65 years). He reported decreased risk of complications in younger and better functional status patients (44).

Despite evidence favoring aggressive surgical resection in carefully selected elderly GBM population, increasing age is associated with a decreased probability of undergoing surgery (25,41,43,45-47). The results of a French phase III trial assessing the significance of surgery on the treatment of patients (age  $\geq 70$ ) with supratentorial malignant gliomas are eagerly awaited (NCT02892708).

### ***RT with standard fractionation (SRT)***

The median survival benefit of postoperative RT for GBM compared with BSC alone (37.5 *vs.* 17 weeks) was first proven by the Brain Tumor Study Group randomized trial (48) with 60 Gy/30 fractions established as the best treatment regimen (49,50). The EORTC trial established postoperative concurrent chemoradiation followed by adjuvant TMZ as the standard of care with statistically significant survival benefit (26).

However, the management of patients who are elderly (>70 years) and/or poor PS remains a gray zone as they were typically deemed not eligible for clinical trials (3). The traditionally used recursive partitioning analysis (RPA) to categorize HGG into different prognostic groups excluded patients age 70 or older (25). Furthermore, retrospective series has shown the overall relative risk of death in GBM patients to be 1.70 and 2.65 for patients in the 70–79 and 80 or older age groups compared with patients in the 60–69 age groups (51). In the absence of high mortality and lack of data, the value of radiotherapy was questioned for patients with poor prognosis.

A shift in paradigm occurred with the French Phase III trial of 81 GBM patients (age  $\geq 70$  years; KPS  $\geq 70$ ) showing statistically significant improvement in median survival with postoperative SRT (50.4 Gy/28 fractions, 29.1 weeks) versus BSC alone (16.9 weeks) without any severe adverse events or differences in QoL and neurocognition (52).

Despite there being level 1 evidence demonstrating the superiority of radiotherapy (RT) over BSC (an absolute gain of 12.2 weeks but without extending acceptable life-years), it is vital to consider the significant time spent in the radiation oncology clinic for treatment. This can have an adverse effect on patients' and their caregiver's QoL, socioeconomic aspects and is perhaps not the best use of limited resources (53). From a logical standpoint, this resulted in efforts to reduce the intensity and duration of the treatment of patients with poor prognosis in order to optimize survival and minimize inconvenience due to treatment, socioeconomic and financial logistics.

### ***Retrospective studies evaluating hypofractionated radiotherapy (HRT) alone***

With the acknowledgment of the benefit of RT compared with BSC, there was a heightened awareness for evaluating contracted regimens to optimize the QoL of patients with poor prognosis and minimize treatment time. Several retrospective studies have been performed to evaluate the efficacy and toxicity outcomes associated with HRT for GBM or HGG (*Table 3*). A few are described below and laid the groundwork for prospective trials. Overall, these studies suggested a benefit from radiotherapy in the poor prognosis group without significant detriment in quality of life (QoL). Furthermore, the hypofractionated regimens seemed to be non-inferior to the conventional regimens (54-58).

### ***Prospective studies evaluating HRT or systemic therapy alone***

Based on promising retrospective data, a number of shorter-course radiation schedules for poor prognosis patients were prospectively evaluated, with the intent to further confirm the previous findings (*Table 4*). The results of these prospective trials reinforced the outcomes seen in retrospective studies. Overall, the hypofractionated regimens were well-tolerated and retained efficacy similar to conventional regimens. Median survival ranged from 4 to 7.6 months (59-63). Hypofractionated intensity-modulated radiotherapy (IMRT) alone was attempted but failed to improve the OS compared with historical control using standard fractionation (64,65). However, the decreased treatment duration from 6 to 2 weeks, using the accelerated schedule, may offer convenient palliation for a select group of patients.

The suggestion of encouraging outcomes by single arm

**Table 3** Selected series of retrospective hypofractionated radiotherapy

Study	Type	Patient selection	No. of patients	Fractionation	Median survival (months)/toxicities
Thomas (54)	Retrospective	Age $\geq 70$ or KPS $\leq 50$ or age 55–70 + KPS 50–70	38	5 Gy $\times 6$	6. No significant toxicities
Kleinberg (55)	Retrospective	All patients	219	3 Gy $\times 17$	RPA class—IV: 13, V: 8, VI: 5. Radiation necrosis in 1 patient
Chang (56)	Retrospective	Median age 65 yr, median KPS 70	59	2.5 Gy $\times 20$	RPA class—IV: 11, V: 7, VI: 5. Radiation necrosis in 3 patients
McAleese (57)	Prospective/ retrospective	Age $\geq 50$ yr and KPS $\leq 90$	92	5 Gy $\times 6$	5. RT related toxicities not specifically reported, Neurologic deterioration in 3% of patients
Lutterbach (58)	Retrospective	Age $\geq 60$ yr	50	3.5 Gy $\times 12$	7.3. No grade $\geq 3$ toxicities

KPS, Karnofsky performance status; RPA, recursive partitioning analysis; RT, radiotherapy.

**Table 4** Selected series of prospective shorter-course radiotherapy regimens

Study	Type	Patient selection	No. of patients	Fractionation	Median survival (months)/toxicities
Hernandez (59)	Prospective	Mean age 52, KPS 57%	14	Accelerated	7.6. No significant toxicities
Bauman (60)	Prospective	Age $\geq 65$ years and/or KPS $\leq 50$	29	3 Gy $\times 10$ (whole brain)	6. RT related toxicities not specifically reported
Slotman (61)	Prospective	All patients	30	3 Gy $\times 14$	8.3. No severe or late toxicities
Ford (62)	Prospective	MRC prognostics score $> 25$	32	3 Gy $\times 12$	4. RT related toxicities not specifically reported
Hulshof (63)	Prospective	Age $\geq 60$ yr or MRC PS $\geq 3$	41, 48	5 Gy $\times 4$ , 7 Gy $\times 8$	5.6, 6.6. RT related toxicities not specifically reported
Sultanem (64)	Prospective	KPS $\geq 60\%$ and postoperative tumor volume $\leq 110$ cm <sup>3</sup> . 2/3 RPA V–VI	25	3 Gy $\times 20$ (GTV = T1 + C), 4 Gy $\times 20$ (PTV = GTV + 1.5 cm), IMRT	9.5. Acute edema in 2 patients. Visual loss in 1 patient
Floyd (65)	Prospective	Age 39–80, KPS $\geq 70\%$	20	5 Gy $\times 10$ (enhancement, residual disease, surgical cavity), 3 Gy $\times 10$ (edema), IMRT	7. Radiation necrosis in 4 patients
Glinski (66)	Prospective	All patients	21	4 Gy $\times 5$ whole brain + 4 Gy $\times 5$ whole brain + 2 Gy $\times 5$ boost. 4-week break after each course	16–17 (from survival curve). Radiation necrosis in 1 patient
Phillips (67)	Prospective	All patients	32 (28 GBM, 4 AA)	3.5 Gy $\times 10$ whole brain	8.7. No late toxicities
Roa (68)	Prospective	Age $\geq 60$ , KPS $\geq 50$ , mean age 72, mean KPS 70	49	2.67 Gy $\times 15$	5.6. RPA class IV: 8.8, RPA class V: 6.9, RPA class VI: 4.8. RT related toxicities not specifically reported
Roa (69)	Prospective	KPS 50–70 or age $\geq 65$ years or both	98	5 Gy $\times 5$ , 2.67 Gy $\times 15$	7.9, 6.4. RT related toxicities not specifically reported

IMRT, intensity modulated radiation therapy; KPS, Karnofsky performance status; RPA, recursive partitioning analysis; GBM, glioblastoma; IMRT, intensity-modulated radiotherapy; RT, radiotherapy; PTV, planning target volume.

**Table 5** Selected series of hypofractionated radiation (HRT) with adjuvant chemotherapy

Study	Type	Patient selection	No. of patients	Treatment	Median survival (months)/toxicities
Minniti (73)	Prospective, phase II	Age $\geq 70$ years and KPS $\geq 60$	43	5 Gy $\times 6$ (2 weeks) + adjuvant TMZ (12 cycles)	OS 9.3, PFS 6.3. Grade 3–4 hematologic toxicity in 28% with TMZ
Muni (74)	Prospective, randomized phase II	Age $>70$ yrs or age $\leq 70$ yrs with KPS $<70$	45	5 Gy $\times 6$ vs. 5 Gy $\times 6$ + adjuvant TMZ	OS 7.3 vs. 9.4. Grade 3–4 hematologic toxicity in 30% with TMZ

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

prospective studies soon led to randomized trials comparing standard fractionation with hypofractionation for patients with HGG. Both the split course hypofractionated regimen and hypofractionated whole brain regimen groups were tolerated well and compared favorably in terms of survival with standard arm (66,67).

The aforementioned results established the safety of hypofractionation, resulting in a need to test the feasibility of this approach in patients with poor prognosis. In a pivotal phase III Canadian study, 100 elderly GBM patients received either SRT (60 Gy/30 fractions) or HRT (40 Gy/15 fractions) to the partial brain. The results of the median survival demonstrated the non-inferiority of HRT (5.6 months) versus SRT (5.1 months) (68). A subsequent phase III trial randomized 98 patients to two different hypofractionated schedules, 25 Gy/5 fractions (1 week) or 40 Gy/15 fractions (3 weeks). Similar outcomes were noted for median survival, PFS or QoL at 4- and 8-weeks post-treatment (69). This trial notably included both elderly as well as poorly performing patients (KPS 50–70). However, it did not include the assessment of any benefit from TMZ chemotherapy.

A randomized phase III German NOA-08 trial looked at the question of TMZ and demonstrated its non-inferiority with a 7-day-on/7-day-off schedule compared with SRT alone (60 Gy/30 fractions) for 412 GBM or AA patients (KPS  $\geq 60$ , age  $\geq 65$  years). The median OS was 9.6 months in the SRT arm compared with 8.6 months in the TMZ arm. Improved median OS was correlated with MGMT promoter methylation (11.9 months) compared with unmethylated tumors (8.2 months). Improved PFS for MGMT methylated tumors treated with TMZ and unmethylated tumors treated with SRT was observed. No differences in health related QOL was detected (70). The same year, a randomized phase III Swedish Nordic trial comparing SRT (60 Gy/30 fractions), HRT (34 Gy/10 fractions), and TMZ (up to 6 cycles) in 342 GBM patients (age  $>60$ ) showed similar median OS for patients

treated with TMZ or HRT (8.4 vs. 7.4 months;  $P=0.12$ ). Notably, TMZ or HRT resulted in significantly better survival compared with SRT for patients over 70 years. Improved OS with TMZ was again noted for patients with MGMT promoter methylation (9.7 vs. 6.8 months,  $P=0.02$ ) (71).

With NOA-08 and Nordic trials only including patients with KPS  $\geq 60$  and ECOG 0–2 respectively, they evaluated treatments for elderly but fit GBM patients. Furthermore, the suggestion of survival benefit by TMZ was largely restricted to MGMT methylated tumors. MGMT promoter methylation is highly predictive for benefit from TMZ. This was in contrast to benefit by RT which was independent of MGMT promoter methylation.

#### *HRT administered with adjuvant chemotherapy*

After Stupp *et al.*'s seminal trial in 2005 and designation of MGMT promoter methylation as a predictor of benefit from TMZ treatment (72), GBM studies on HRT for poor prognosis patients started including TMZ (Table 5). Due to toxicity concerns with concurrent chemotherapy, initial hypofractionation studies were performed with adjuvant chemotherapy. Both trials reported an independent significant association of KPS with survival. Notably, no worsening of QoL was noted other than progressive exacerbation of fatigue (73,74).

#### *HRT administered with concurrent chemotherapy*

The safety of HRT with adjuvant chemotherapy prompted studies with hypofractionation and concurrent chemotherapy. Lim *et al.* retrospectively reviewed 33 GBM patients (age  $\geq 70$  years or risk factors including poor PS, rapidly progressive disease or biopsy only) who received HRT (median RT dose 45 Gy/15 fractions) with concurrent TMZ. With a median age of 66 and tolerable side-effects, the median OS was 10.6 months (75).

**Table 6** Selected series of hypofractionated radiation (HRT) with concurrent and adjuvant chemotherapy

Study	Type	Patient selection	No. of patients	Arms	Median survival (months)/toxicity
Panet-Raymond (76)	Retrospective	All patients. Median age 63. 75% RPA V/VI	35	3 Gy ×20 to GTV and 2 Gy ×20 to PTV with concurrent and adjuvant temozolomide (6 cycles)	14.4. Grade 3–4 nausea/vomiting in 1 patient
Terasaki (77)	Prospective	All patients, KPS ≥50. Median age 61, median KPS 60	26	3 Gy ×15 with concurrent and adjuvant temozolomide (12 cycles)	15.6. Grade 4 neutropenia: 3 patients, grade 4 thrombocytopenia: 1 patient
Minniti (78)	Prospective, phase II	Age ≥70 years, KPS ≥60	71	2.67 Gy ×15 with concurrent and adjuvant temozolomide (12 cycles)	12.4. Grade 3–4 hematologic toxicity in 10 patients, grade 3 fatigue in 4 patients, grade 3 cognitive disability in 1 patient
Ohno (79)	Retrospective	Age ≥75, KPS ≥50, median age 80, 37% KPS 50–60	30	3 Gy ×15 and concurrent temozolomide and adjuvant temozolomide (12–24 cycles) or 3 Gy ×15 and adjuvant temozolomide/bevacizumab	12.9. Grade 3–4 toxicities: leukopenia in 15 patients (50%), anorexia in 4 patients (13%), hyponatremia in 3 patients (10%)
Perry (80)	Prospective, phase III	Age >65 yrs, ECOG 0–2, median age 73	562	2.67 Gy ×15 vs. 2.67 Gy ×15 with concurrent and adjuvant temozolomide (12 cycles)	7.6 vs. 9.3, methylated MGMT: 7.7 vs. 13.5 (P=0.001), unmethylated MGMT: 7.9 vs. 10 (P=0.055). Grade 3–4 hematologic toxicity: 25% in chemoradiation vs. 9% in radiation alone arm

KPS, Karnofsky performance status; RPA, recursive partitioning analysis; MGMT, O6-methylguanine-DNA-methyltransferase; PTV, planning target volume.

### **HRT administered with concurrent and adjuvant chemotherapy**

With Stupp's trial establishing standard of care for GBM treatment, several studies were published to assess the safety and efficacy of postoperative HRT with concurrent and adjuvant TMZ (*Table 6*). Retrospective and single arm prospective GBM studies suggested promising median OS (12.4 to 15.6 months) with acceptable toxicity and neurocognition (76–78). Ohno *et al.* recently reported on 30 GBM patients (age ≥75, KPS ≥50) treated with either HRT (45 Gy/15 fractions) with concurrent and adjuvant TMZ or a combination of adjuvant TMZ and bevacizumab. The reported median OS, PFS and time for KPS score to decrease below 60 were 12.9, 9.9 and 7.9 months, respectively (79).

A landmark phase III (CE.6) randomized trial compared HRT alone (40 Gy/15 fractions) *vs.* HRT (40 Gy/15 fractions) with concurrent daily TMZ and adjuvant TMZ for 12 cycles in 562 GBM patients (age ≥65) (80). Unlike the Stupp trial, a short course of radiation and concurrent

TMZ were delivered but the number of cycles of adjuvant TMZ was higher. Median age of patients was 73 years. Chemoradiation resulted in a significant improvement in median OS (9.3 *vs.* 7.6 months, P<0.0001) and PFS (5.3 *vs.* 3.9 months, P<0.001). Importantly, this progress was accomplished with acceptable hematologic toxicities. Despite gastrointestinal toxicity being slightly higher in the chemoradiation arm, there was no substantial impact on QoL. Notably, this trial only included patients with ECOG PS-0–2. To date, this regimen has not been directly compared with the standard 6-week radiation regimen with concurrent and adjuvant TMZ in the elderly population.

### **HRT with chemotherapy versus standard radiotherapy (SRT) with chemotherapy**

There are no randomized trials that have directly compared HRT + TMZ with SRT + TMZ. However, there have been retrospective studies comparing the efficacy and toxicity of the two regimens with mixed results (*Table 7*). Minniti *et al.* and Arvold *et al.* reported no significant differences in

**Table 7** Selected series of hypofractionated radiation (HRT) with temozolomide compared with standard radiation (SRT) with temozolomide

Study	Type	Patient selection	No. of patients	Arms	Median survival (months)/toxicity
Minniti (81)	Retrospective	Age $\geq$ 65 years, KPS $\geq$ 60	243	2 Gy $\times$ 30 vs. 2.67 Gy $\times$ 15. Both with concurrent and adjuvant temozolomide	12 vs. 12.5. Higher grade 2–3 neurologic toxicity, higher steroid requirement and lowering of KPS scores in standard arm vs. hypofractionated arm
Arvold (82)	Retrospective	Age >65 yrs	135	2 Gy $\times$ 30 vs. 2.67 Gy $\times$ 15. Both with concurrent temozolomide	No difference in survival
Gzell (83)	Retrospective	Age 65–75	69	2 Gy $\times$ 30 vs. 2.67 Gy $\times$ 15. 70% received temozolomide	12. 15 (SRT) vs. 9 (HRT), 13 (TMZ) vs. 7 (no temozolomide)
Chang-Halpenny (84)	Retrospective	Age >65	129	2 Gy $\times$ 30 vs. 3.5 Gy $\times$ 10. Both with concurrent temozolomide	13 vs. 5.4

KPS, Karnofsky performance status; SRT, standard radiation therapy; HRT, hypofractionated radiation therapy; TMZ, temozolomide.

survival between the two regimens. Of note, patients in the HRT + TMZ arm in the latter review were significantly older and had worse baseline PS (81,82). In contrast, Gzell *et al.* and Chang *et al.* have reported worse outcomes with HRT + TMZ compared with SRT + TMZ. Again, patients treated with HRT + TMZ in the latter study had significantly worse prognostic factors at baseline that could be the reason for the observed inferior outcomes (83,84).

#### **Patients with poor performance status**

The patients with poor PS have been largely excluded from trial. Earlier sections have touched upon a few studies that included this subset. Although there is a lack of high-quality evidence, we will attempt to evaluate available treatment options for patients with poor PS. These include radiation with standard fractionation (SRT) alone, hypofractionated radiation (HRT) alone, concurrent chemoradiation with either SRT or HRT, and chemotherapy alone. For patients with KPS  $\leq$ 50, the benefit in survival as well as PS by radiotherapy (1.5–6 Gy fraction sizes) was shown by Marina and colleagues (85). Similarly, for patients with KPS  $\leq$ 50, Bauman *et al.* failed to show a benefit for protracted treatment compared to a shorter palliative course (30 Gy/10 fractions whole brain). However, in this study, the patient groups were not fully balanced at baseline, with significantly older patients receiving the longer radiation course (60).

A logical solution to improve tolerance to therapy for these patients would be sequential delivery of treatment. The Lamborn analysis and NCDP data (21,86) both showed disappointing results although the results of the former study are increasingly dated and the latter one has the

drawbacks associated with a database review. Of note, HRT was either not used or not assessed. Mixed results in terms of survival for patients with KPS <70 have been reported when combining SRT with concurrent chemotherapy (87,88). However, another study of patients with KPS <70 reported promising survival and acceptable toxicity with HRT and concurrent TMZ (89). Improved efficacy was also reported by TMZ alone *vs.* BSC for patients with KPS <70 (90).

Finally, a prospective study of patients (median KPS 70) reported similar survival for a 60 Gy 6-week and 40-Gy 3-week course with less steroid dependency associated with HRT (68). The same group then showed equivalence in survival and QoL between 25 Gy/5 fractions and 40 Gy/15 fractions for elderly and/or frail patients (91).

#### **RT target volume delineation**

Variation in target volume design exists for both standard and HRT. RTOG uses a 2-phase approach, with an initial phase targeting edema (T2/FLAIR hyperintense), gross residual tumor (T1-enhancing) and surgical cavity followed by a boost to the gross tumor and cavity. This is in contrast to EORTC single-phase approach, directed at enhancing tumor plus cavity with a wide margin (without specifically targeting edema) for the entire treatment (26). Retrospective studies suggest small 5 mm clinical target volume (CTV) margins may not exacerbate the risk of marginal failure. Majority of these plans had 3–5 mm planning target volume (PTV) margin (92). *Table 8* summarizes the margins used in cooperative group in clinical trials as well as hypofractionated series.

Although edema is thought to reflect infiltrative



**Table 8** Target volume definitions utilized by various cooperative groups and series

Cooperative groups	One/two phase	CTV (initial)	CTV (boost)	PTV
ABTC (92)	Two-phase: 46+14=60 Gy	T2 + T1E + cavity +5 mm	Cavity + T1E +5 mm	Institution specific, generally 3–5 mm
EORTC (26)	One-phase: 60 Gy in 30 fractions	Cavity + T1E +20–30 mm	–	Institution specific, generally 5–7 mm
Alliance (93)	Two-phase: 50+10=60 Gy	T2 + T1E + cavity +20 mm to block edge	Cavity + T1E +20 mm to block edge	PTV addressed in CTV expansions
NRG (94)	Two-phase: 46+14=60 Gy	T2 + T1E + cavity +20 mm	Cavity + T1E +20 mm	3–5 mm
Nordic Clinical Brain Tumor Study Group (54)	One-phase: 34 Gy in 10 fractions	T1E +2 cm*	Not applicable	Institution specific*
International Atomic Energy Agency (68,69)	One-phase: 40.05 Gy in 15 fraction or 25 Gy in 5 fractions	T1E + cavity +20 mm	Not applicable	5 mm
Canadian Cancer Trials Group (CCTG), European Organization for Research and Treatment of Cancer (EORTC) Trans-Tasman Radiation Oncology Group (TROG) (80)	One-phase: 40.05 Gy in 15 fractions	T1E + cavity +15 mm	Not applicable	Institution specific, generally 5 mm
Ohno <i>et al.</i> (79)	Two-phase: 30+15=45 Gy	T2 + T1E + cavity +15 mm	Cavity + T1E +15 mm	5 mm

\*Per Thomas 1994. T1E, residual T1-enhancing abnormality; GTV, gross target volume; CTV, clinical target volume; PTV, planning target volume.

tumor (95), similar patterns of failure are reported with both approaches (96). Ninety percent patients failed centrally and in-field in both treatment plans. CTV delineation based on a 2-cm margin around contrast-enhanced residual tumor and surgical cavity rather than on peritumoral edema did not seem to alter the central pattern of failure (96). Similar patterns were observed in another study that included concurrent and adjuvant TMZ. Central/in-field and outside-field recurrences occurred in 91% and 5.4% of unmethylated patients, and 64% and 31% of methylated patients, respectively ( $P=0.01$ ). Central recurrence within high dose region predominates regardless of target volume design. The median volume of brain receiving high dose radiation was significantly smaller for plans based on residual tumor and cavity plus 2 cm ( $P=0.0001$ ) (97).

The incidence of neurotoxicity is dependent on the volume of brain parenchyma—a late-responding tissue—irradiated to a high dose. If HRT is used to treat GBM, the potential for major acute (edema) and late complications (necrosis and damage to optic chiasm and brainstem) has to be considered, especially when conformal radiotherapy techniques are not used or available. Based on the data

available in the literature, it seems to be appropriate to use a 2 cm margin around residual tumor and cavity as the CTV.

### Other modalities

Besides surgery, radiation and TMZ, other therapies may play a role in palliative treatment of HGG patients with poor prognosis. Some have failed while others are still being investigated. ARTE, a phase II trial, randomized 75 GBM patients (age  $\geq 65$  yrs) to HRT (40 Gy/15 fractions) alone or HRT (40 Gy/15 fractions) with bevacizumab. With a median OS of 12 months in both arms, the addition of bevacizumab did not improve survival (98). Another non-randomized trial by EORTC Brain Tumor Group is actively accruing elderly GBM or AA patients (age  $>65$ , KPS  $\geq 60$ ) and will be evaluating outcomes for the combination of novel multikinase inhibitor TG02 with either TMZ or HRT (39.9 Gy/15 fractions) (99).

Tumor-treating fields (TTF) is used for the treatment of newly diagnosed and recurrent GBM. It is an FDA-approved device consisting of a set of insulated electrodes that must be placed over a shaved scalp. The electrodes create very low intensity alternating electrical fields that

are thought to selectively target proliferating cells through antimetabolic mechanisms. For upfront GBM treatment, TTF starts with adjuvant TMZ phase. The EF14 trial for newly diagnosed GBM enrolled patients with an age range from 20 through 83 (median age =57 years), although age-specific outcomes have not been published to date (100). TTF can be considered as a potential treatment option regardless of age but the patient's KPS and estimated survival should determine the appropriateness of its use given the associated cost, treatment duration, and psychosocial factors.

## Summary

The concept of radical/curative *vs.* palliative radiation can be blurred in the management of HGG (including GBM) patients as they are seldom cured. There is a lack of granularity within our current repertoire of how we describe radiation treatment intent: curative versus palliative. In medical oncology, there are other terms including life prolonging therapy, which may be more akin to how we approach HGG treatment.

The current standard of care treatment for HGG with standard fractionation radiation course still provides the best though suboptimal outcomes for the better prognosis patients (*Table 2*). In patients with shorter expected survival due to poor prognosis (*Table 2*), radiation with standard fractionation is unlikely to provide a meaningful benefit and a hypofractionated course of RT delivering a much lower BED yields similar survival as shown by studies mentioned earlier.

In this review, the concept of palliative radiation for a patient is based on the estimated poor survival of the patient. Thus, a less intensive and better tolerated course of radiation (hypofractionated radiation) delivering a less than radical dose to such a patient is regarded as palliative radiation. In fact, one can argue that even radiation with standard fractionation is palliative in such a patient with poor prognosis but will do more harm as it is worse tolerated, and the patient will be spending a bigger proportion of his/ her remaining time getting treatment. As many of us may believe we are prolonging survival but not necessarily curing patients, we are selecting a radiation dose/fractionation that is tailored to expected life expectancy. We also acknowledge that palliative is not solely defined by using a hypofractionated regimen. However, our review essentially focuses on the evidence behind alternate dose/fractionation schemes for patients with poorer life expectancy/performance status.

Although one can argue that any radiotherapy in HGG or more specifically GBM, is palliative, but for the sake of simplicity, we are referring to only hypofractionated regimens as palliative. Typically, upfront palliative treatment is offered to patients with poor prognosis. There has been no clear standard of care for the treatment of HGG in patients with poor prognosis for the following reasons: (I) lack of data as these patients were largely excluded from trials, (II) multiple factors (*Table 2*) affecting prognosis and their interactions with each other, (III) traditional caveats associated with retrospective reviews, (IV) lack of clear definition of prognostic factors and their subjective interpretation and (V) differences in tumor biology.

The outcomes from surgical studies favor maximal safe resection, regardless of age. However, these studies provide limited data related to potential surgical complications, neurocognitive status and time to functional recovery after varying levels of resections. With such an aggressive disease, maintaining QoL and preventing new permanent neurological deficits are important factors to consider before embarking on a surgical plan for these patients. Optimal surgery can have a dramatic effect on a patient's functional status which subsequently alters their KPS score. This improvement in post-operative KPS has been associated with increased OS and has superior predictive value compared to pre-operative KPS score (101). In absence of randomized studies, the optimal surgical management in these patients should be based on careful evaluation of metrics such as neurologic and geriatric assessment, speed of clinical decline, operative risk and estimation of prognosis.

Although SRT may represent a viable treatment option for select elderly fit patients (age 60–70), results of phase III studies comparing SRT and HRT regimens demonstrate benefit in terms of similar survival and decreased treatment duration with HRT. The toxicity of hypofractionation must, however, be considered. With conservative margins and advanced radiation techniques routinely employed in practice, conformal and precise radiation doses to the target can be delivered while risk of neurocognitive decline is lowered with reduced exposure of the adjacent normal brain parenchyma.

The assessment of neurocognitive and functional status and maintenance of QoL is of particular relevance to ensure optimal outcomes. Studies have shown no significant worsening of neurocognition and QoL with radiation. McAleese *et al.* reported improvement or stability in Barthel scores of 68% patients with 30 Gy/6 fraction regimen (57).

In a trial comparing SRT versus HRT, KPS scores were not significantly different between groups (68). Moreover, the HRT resulted in decreased corticosteroid requirement. Notably, 26% of patients receiving SRT *vs.* 10% receiving HRT had treatment interruptions due to acute toxicity. There was no significant change in global health status and functioning scales between SRT and HRT in the Nordic study. However, cautious interpretation is required due to low completion rates of these QoL questionnaires (71). Similar mean global QoL scores at 8 weeks were reported by both 40 Gy/15 fractions and 25 Gy/5 fractions regimens (69).

In terms of chemotherapy, TMZ is an efficacious and tolerated treatment for elderly GBM patients. It is correlated with significant improvement in KPS, neurocognitive evaluation and QoL questionnaires. However, approximately 20% patients experience grade 3–4 hematologic toxicity. TMZ, compared with SRT, results in improved survival in elderly patients with MGMT methylated tumors. The benefit from TMZ is most prominent in GBM patients with methylated MGMT promoter. The outcomes of the NOA-08 and Nordic trials support consideration of TMZ alone for MGMT methylated, elderly patients, especially if radiation delivery is impractical or contraindicated (70). Furthermore, chemotherapy alone, as compared to radiation, has the benefit of requiring less frequent and fewer total trips to a medical provider.

Although SRT with concurrent and adjuvant TMZ is a reasonable option in patients with good PS and under the age of 70, concerns remain about the length of treatment as well as PS and under the age of 70, treatment-related neurotoxicity resulting in worsening of QoL and functional status remains a concern. Based on the results of the CE.6 trial, elderly patients with MGMT promoter methylation should be offered HRT with concurrent and adjuvant TMZ. Although MGMT methylation is highly predictive for benefit from TMZ, interpretation of this benefit in the case of MGMT-unmethylated tumors remains controversial, with recent evidence indicating some benefit from combined-modality treatment (80,102). There was no reduction in benefit from TMZ with increasing age. The survival advantage of TMZ was conferred without a sacrifice in QoL and with manageable toxicity. Many may favor the hypofractionated protocol in context of these results and an EORTC subgroup analysis failing to show survival benefit with standard chemoradiation in patients over the age of 65 ( $P=0.340$ ) (103).

Patients deemed unfit for chemoradiation should be

treated with HRT or TMZ based on MGMT promoter methylation status. These patients are treated with HRT especially for tumors without MGMT methylation or unknown promoter status. The HRT regimen of 34 Gy/10 fractions or 40 Gy/15 fractions are most commonly employed, but an attractive alternative is 25 Gy/5 fractions, particularly in terms of treatment duration, intolerance to concurrent chemotherapy and completion in less than a week (69). This further hypofractionation does not seem to compromise survival but has a potential to cause neurocognitive side effects which will assume more relevance once other treatment options allow long-term survival in elderly GBM patients.

In selecting patients for combined modality therapy (CMT), the importance of assessing the patient's performance status is crucial. Some studies have highlighted the significance of PS as being the most relevant factor for selecting patients for CMT (73,74). CE.6 included elderly patients but only with PS 0–1 (80). With the lack of data, the decision to embark on a specific treatment option needs to be taken while considering not only PS and age but other prognostic factors as mentioned earlier.

Currently, there are two nomograms available to assist in treatment decision making by individualizing cancer prognosis in GBM. Both are, however, based on standard fractionation radiotherapy. The first is an internally and externally validated nomogram developed by using data from NRG Oncology trials, 0525 and 0825. Increasing age, male gender, lower KPS, sub-total resection, and unmethylated MGMT status were associated with poor survival (104). However, it did not include important prognostic factors, such as receipt of concurrent chemoradiation and IDH mutation status. Gittleman *et al.* then developed a nomogram for IDH-wt GBM and found that younger age, female sex, gross total resection, concurrent radiation/TMZ, high KPS and MGMT methylation were associated with better survival (31).

Based on our review of the literature, we make the following recommendations for HGG treatment (*Table 9*):

- (I) Age <65, KPS  $\geq 60$ , expected median survival >6–8 months: consider standard radiation with concurrent and adjuvant TMZ and alternating electric field therapy.
- (II) Age  $\geq 65$ , KPS  $\geq 60$ , expected median survival >6–8 months, MGMT promoter methylated: consider standard radiation with concurrent and adjuvant TMZ and alternating electric field therapy or hypofractionated radiation with

Table 9 Recommendations for treatment of high-grade glioma (HGG)

Age (years)	KPS [1–100]	Expected survival (months)	MGMT promoter methylation status	Management
<65	≥60	>6–8		SRT + concurrent & adjuvant TMZ + EFT
≥65	≥60	>6–8	Positive	SRT + concurrent & adjuvant TMZ + EFT or HRT + concurrent & adjuvant TMZ
≥65	≥60	>6–8	Negative or unknown	SRT + concurrent & adjuvant TMZ + EFT. HRT + concurrent & adjuvant TMZ is an option
≥65	≥60	<6–8	Positive	HRT + concurrent & adjuvant TMZ
≥65	≥60	<6–8	Negative or unknown	HRT + concurrent & adjuvant TMZ or HRT alone
≥65	<60	<6–8	Negative or unknown	HRT alone
≥65	<60	<6–8	Positive	TMZ alone
<65	<60	>6–8		HRT +/- concurrent & adjuvant TMZ
<65	<60	<6–8		HRT alone or TMZ alone

SRT, standard radiation therapy; HRT, hypofractionated radiation therapy; TMZ, temozolomide; EFT, electric field therapy.

concurrent and adjuvant TMZ.

- (III) Age ≥65, KPS ≥60, expected median survival >6–8 months, MGMT promoter unmethylated/unknown: consider standard radiation with concurrent and adjuvant TMZ and alternating electric field therapy. Hypofractionated radiation with concurrent and adjuvant TMZ is an option.
- (IV) Age ≥65, KPS ≥60, expected median survival <6–8 months, MGMT promoter methylated: consider hypofractionated radiation with concurrent and adjuvant TMZ.
- (V) Age ≥65, KPS ≥60, expected median survival <6–8 months, MGMT promoter unmethylated/unknown: consider hypofractionated radiation with concurrent and adjuvant TMZ or HRT alone.
- (VI) Age ≥65, KPS <60, expected median survival <6–8 months, MGMT promoter unmethylated/unknown: consider HRT alone.
- (VII) Age ≥65, KPS <60, expected median survival <6–8 months, MGMT promoter-methylated: consider TMZ monotherapy.
- (VIII) Age <65, KPS <60, expected median survival >6–8 months: consider HRT +/- concurrent or adjuvant TMZ.
- (IX) Age <65, KPS <60, expected median survival <6–8 months: consider HRT alone or TMZ alone.

Current NCCN guidelines (V2.2020) recommend HRT with the optional addition of concurrent or adjuvant TMZ

for GBM patients with KPS <60 and age ≤70 and HRT or TMZ alone for KPS <60 and age >70. The addition of TMZ to HRT/SRT (methylated) and TMZ to SRT (unmethylated) becomes a category 1 recommendation for patients with KPS ≥60 and age >70. The American Society for Radiation Oncology's (ASTRO) practice guidelines [endorsed by American Society of Clinical Oncology's (ASCO)] from 2016 recommend HRT alone, TMZ alone or BSC for poor performance status (KPS <60) patients and consideration for RT with concurrent and adjuvant TMZ in patients (age ≥70 years) with KPS ≥50 (105).

### Future directions

It is important that further research continues to explore the biology and development of individualized protocols for optimal management of HGG. Future trial designs should include primary end points to evaluate the tolerance of various therapeutic modalities, potential impact on QoL with TMZ *vs.* HRT alone and striving for an acceptable non-inferiority margin in OS as a tradeoff for shorter time on treatment.

An area of active research includes the use of appropriate radiation response modulators. The final results of a UK study of elderly HGG patients (NCT01602588) assessing the addition of hydroxychloroquine to radiation (30 Gy/5 fractions) are eagerly awaited (106). With a deeper understanding of the biology of HGG and well-designed trials, the hope is to personalize and optimize palliative treatment for advanced patient care.

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