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REVIEW ARTICLE

Modified optimal fractionation for poor prognosis malignant gliomas: An elusive search

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Abstract
The prognosis of malignant gliomas has not changed much over the last few decades despite refinements in neurosurgical techniques, high-precision radiotherapy, and newer chemotherapeutic agents. The median survival of poor prognosis malignant gliomas (older and/or poor performance status patients) still remains in the range of 6–9 months following maximal safe resection and postoperative conventionally fractionated adjuvant radiotherapy with or without chemotherapy. However, six weeks of daily radiotherapy does seem inappropriate in relation to the short expected survival time in this subset and there is an increasing emphasis on reducing the overall treatment time and the number of hospital visits by such patients. This can be achieved either by accelerated radiotherapy or by hypofractionated radiation, both of which are equivalent to conventional fractionation in terms of palliative effect and survival, as in discussed in this review. Despite enough evidence, such alteration of fractionation has not gained widespread acceptance by the oncologic fraternity. This review has been conducted to collate the evidence that could help shift the paradigm from conventional to modified fractionation in poor prognosis malignant glioma patients.

Introduction

Gliomas are the commonest primary neoplasms of the central nervous system (CNS), comprising over 50% of the tumors in adults [1]. In the year 2000, the estimated number of new cases of primary CNS neoplasms was 16 500 with an estimated death of 13 000 in the US alone [2]. High-grade tumors (Kernohan & Sayre [3] Grade III and IV astrocytomas), i.e. anaplastic astrocytomas (AA) and glioblastoma multiforme (GBM) respectively account for the majority of astrocytic tumors and are referred to as malignant gliomas. Less common entities such as anaplastic oligodendrogliomas, anaplastic oligoastrocytomas, gemistocytic tumors, and gliosarcomas are also often included in the analysis of malignant gliomas.

The standard treatment for these tumors has been maximal safe surgical resection followed by postoperative adjuvant conventionally fractionated external beam radiation [4–6]. Although a recent meta-analysis [7] of randomized controlled trials reported a modest survival advantage with adjuvant chemotherapy (CTh), a large randomized controlled trial by the Medical Research Council (MRC) failed to demonstrate any such survival benefit [8]. The pre-treatment prognostic factors that influence survival include age, performance status, extent of surgical resection, histology Gy, and a decrease in tumor size following radiotherapy (RT). Based on such clinico-pathologic prognostic factors, malignant gliomas [9,10] can be broadly classified into:

1. Favorable prognosis: young patients with good performance status where the median survival after optimal debulking and radical radiotherapy is 12–24 months.
2. Poor prognosis: the elderly or those with poor performance status where the median survival is 6–9 months despite aggressive surgery and radiation.

Ever since the advent of fractionated external beam radiotherapy, the prognosis for malignant gliomas has not changed substantially. Temozolomide had previously shown some improvement in progression-free survival (PFS) and the quality of life (QOL) in patients

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with recurrent GBM [11], but only recently has demonstrated significant improvement in overall survival for newly diagnosed malignant gliomas [12,13] when used in the concurrent and adjuvant setting.

Rationale for modified fractionation

Conventional fractionated radiotherapy (55–60 Gy in 30 fractions over 6 weeks), however, still remains the mainstay of treatment after surgical debulking in the majority of centers worldwide (Figure 1). Nevertheless this six weeks of daily radiotherapy does seem inappropriate in relation to the short expected survival time in the poor prognosis subset. An acceptable schedule for such patients should be short, well tolerated and convenient for the patients as well as the caregivers without compromising on its efficacy. Although a consensus seems to emerge on reducing the overall treatment time (OTT) and/or the number of hospital visits by such patients, there is no unanimity on how to go about it. There are two general premises to achieving this. The first suggests that since cancer involves biological entities that mutate at very high rates, the treatment should be instantaneously effective otherwise the dynamics of evolution will create new forms with relatively resistant clones. Hence the concept of accelerated radiotherapy (Figure 1). The basic rationale of acceleration is that reduction in OTT decreases the opportunity for tumor cell regeneration during treatment and therefore increases the probability of tumor control for a given dose. The second premise is to use a large dose per fraction for a small number of fractions to achieve a biologically equivalent dose (BED) that would achieve similar tumor control probability. A recent study on GBM cell lines [14] has suggested that glioblastomas harboring p53 mutations behave more like late responding tissues and have a low α/β ratio and would therefore be relatively resistant to conventional fractionation. According to this a few large dose fractions, i.e. hypofractionated radiotherapy (Figure 1), would be more apt for such tumors. Also the use of hypofractionation would entail lesser number of hospital visits for these patients. Therefore the paradigm could shift from conventional to altered fractionation. It is in keeping in view the aforesaid premises that a review of modified fractionation in poor prognosis malignant gliomas was carried out.

Methods

Literature search strategy Gy

Published data for this review was identified by searching MEDLINE, CANCERLIT, EMBASE,

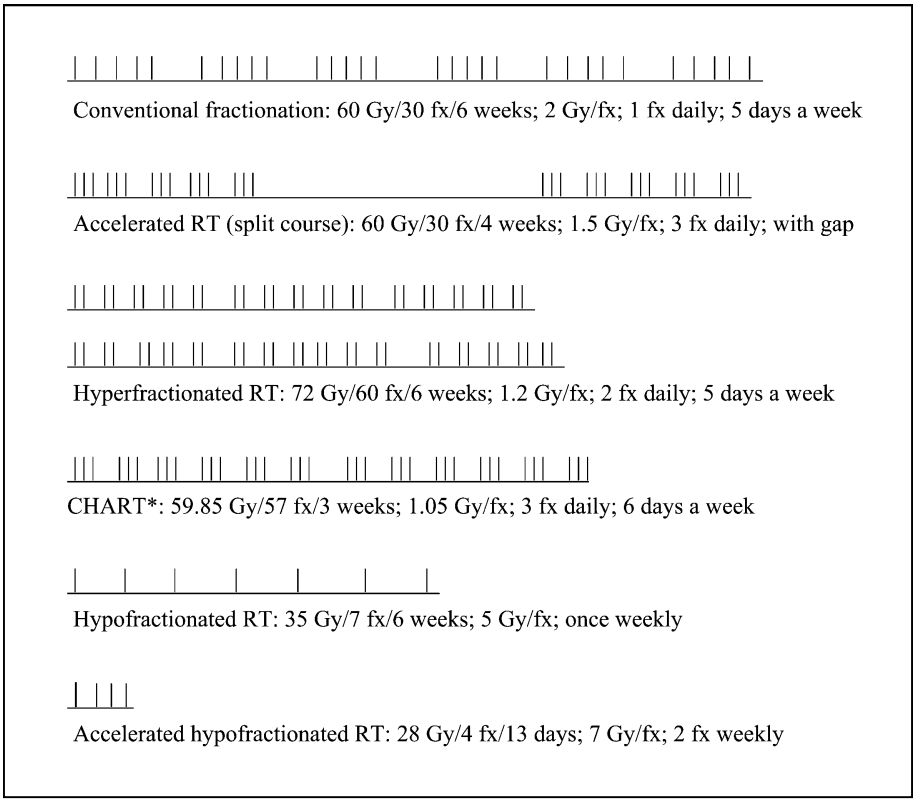

Figure 1. Different fractionation schemes in malignant gliomas.

and The Cochrane Library (Issue 1, 2003) databases with no language restrictions. "Malignant gliomas", OR "high grade gliomas", OR "glioblastomas", was combined with "radiotherapy", "dose fractionation", and "chemotherapy" as medical subject heading (MeSH) terms and each of the following phrases used as text words: "poor prognosis", "accelerated radiation", "hypofractionation", and "sensitizers". Relevant cross-references from the selected articles were also considered. Only prospective studies with more than 20 patients were included. Trials using purely hyperfractionation without any form of acceleration were excluded.

Studies using predominantly accelerated RT

Trials using accelerated RT

All the non-randomized prospective trials [15–25] using accelerated RT purely or its variants such as dose-escalation studies using accelerated RT, concomitant boost RT, or accelerated-hyperfractionated radiation (AHF-RT) are summarized in Table I. Most of these trials were Phase I or II studies with relatively small sample size using different dose schedules (including dose/fraction and number of fractions/day). The median OTT was 4.5 weeks (range 1.5–6 weeks) causing a median acceleration of 2 weeks.

Randomized trials using accelerated/accelerated hyperfractionated RT

There are seven prospective randomized controlled trials [26–29,31–33] comparing conventional fractionation with accelerated radiation in malignant gliomas, with or without sensitizers, albeit with conflicting results (Table II).

In the first of these by Simpson [26] et al., 134 patients were randomly assigned to three different radiation schedules. In the initial phase a total dose of 30 Gy was delivered with 0.48–1.43 Gy/fraction; 1–3 fractions per day in 1–3 weeks. The dose was increased to 40 Gy in the second phase without changing the dose per fraction or the number of fractions, thereby increasing the OTT to 1.5–4 weeks. In the final phase, the OTT was again reduced to 1–3 weeks, delivering 0.63–1.93 Gy/fraction, 1–3 fractions per day to a TTD of 40 Gy. Thus 91 patients received accelerated RT (3 fractions daily with 0.48–1.93 Gy fraction) to a dose of 30–40 Gy in 1–3 weeks. Conversely, 43 patients received conventional RT (one fraction daily with 1.43–1.93 Gy/fraction) to a TTD of 30–40 Gy in

Table I. Non-randomized trials using accelerated RT in malignant gliomas.

Author (ref)	No of pts (n)	TTD (Gy)	Fx/d (#)	Dose/fx (Gy)	OTT (wk)	MS (mth)	1-yr survival	Remarks
Trials using purely accelerated RT								
Douglas (15)	30	56–70 Gy	3 #	1 Gy	3.5–4.5 wk	9 mth	NA	10 Gy boost
Keim (16)	38	60 Gy	3 #	1.6 Gy	2.5 wk	9.5 mth	NA	2.8 Gy on Sat
			1 #	2.8 Gy				
Shenouda (17)	42	44 Gy WBRT+	1 #	2 Gy	4.5 wk	13 mth	50%	16 Gy as conc
		16 Gy	2 #	2 Gy				omitant boost
Brada (18)	211	55 Gy	2 #	1.6 Gy	3 wk	10 mth	38%	–
Trials of dose escalation with accelerated RT								
Fulton (19)	280	61.4–80 Gy	3 #	0.9–1 Gy	4.5–5.5 wk	10.5 mth	NA	–
Gonsalez (20)	15	42 Gy	3 #	2 Gy	9 days			
	17	48 Gy	3 #	2 Gy	10 days	8.7 mth	NA	No diff. at all dose
	18	54 Gy	3 #	2 Gy	11 days	combined		levels
	16	60 Gy	3 #	2 Gy	12 days			
Fitzek (21)	23	90 CGE	NA	NA	NA	20 mth	NA	Better
Trials using AHF-RT								
Buatti (22)	70	60 Gy	2 #	1.5 Gy	4 wk	13.8 mth	16% at 2yr	Stereotactic/implant boost
Bese (23)	36	59.85 Gy	3 #	1.05 Gy	3 wk	13 mth	–	22% at 2–yr
Lutterbach (24)	149	54 Gy	3 #	1.5 Gy	3 wk	8.8 mth	31%	–
Neider (25)	34	78 Gy	2 #	1.3 Gy	4 wk	7–10 mth	19–29%	–
	92	60 Gy	2 #	1.5 Gy	4 wk			

TTD = total tumor dose; OTT = overall treatment time; Fx = fractions; d = day; MS = median survival; AHF-RT = accelerated hyperfractionedRT; NA = not available; CGE = cobalt gray equivalent.

Table II. Randomized trials of accelerated RT vs. conventional RT in malignant gliomas.

Author (ref)	No. of pts (n)	TTD (Gy)	Fx/day	Dose/Fx (Gy)	OTT (week)	MS (mth)	1-yr survival	Remarks
Simpson (26)	CF = 43	30–40 Gy	1 #	1.43–1.9 Gy	3–4 wk	7.2 mth	30%	NS
	AF = 91	30–40 Gy	3 #	0.48–1.9 Gy	1–4 wk	9.6 mth	30%	
Payne (27)	CF = 79	50 Gy	1 #	2 Gy	5 wk	10 mth	45%	NS
	AHF = 78	36–40 Gy	4 #	1 Gy	2 wk	10.6 mth	44%	
Shin (28)	CF = 34	50 Gy	1 #	2 Gy	5 wk	9 mth	NA	NS, but trend +
	AF = 35	50 Gy	3 #	0.89 Gy	4 wks	13 mth	NA	
Shin (29)	CF = 38	58 Gy	1 #	1.8–2 Gy	6 wk	6.7 mth	20%	$p < 0.001$ for AF
	AF = 43	61.4 Gy	3 #	0.89 Gy	4.5 wk	9.7 mth	41%	
	AF+M = 43	61.4 Gy	3 #	0.89 Gy	4.5 wk	12.1 mth	45%	
Ludgate (31)	CF = 34	50 Gy	1 #	2 Gy	5 wk	8 mth	32%	NS, but trend+
	AHF = 42	57.6 Gy	3#	0.76 Gy	4 wk	11.5 mth	54%	
Horiot (32)	CF	60 Gy	1#	2 Gy	6 wk	Combined	14% at 2yr	NS
	AF	60 Gy	3#	2 Gy	4 wk	11 mth		
	AF+M (340 pts)	60 Gy	3#	2 Gy	4 wk			
Prados (33)	CF = 58	59.4 Gy	1 #	1.8 Gy	6.5 wk	37 wk	NA	NS
	CF+D = 59	59.4 Gy	1 #	1.8 Gy	6.5 wk	44 wk	NA	
	AHF = 57	70.4 Gy	2 #	1.6 Gy	4.5 wk	40 wk	NA	
	AHF+D = 57	70.4 Gy	2 #	1.6 Gy	4.5 wk	42 wk	NA	

CF = conventional fractionation; AF = accelerated fractionation; AHF = accelerated hyperfractionated radiation; M = misonidazole; D = Difluromethylornithine; NA = not available; NS = non-significant.

3–4 weeks. The 1-year survival and toxicity was not significantly different amongst any of the randomized groups. Although the authors concluded that it is possible to reduce the OTT without significant complications, it is difficult to draw firm conclusions from this study. The total dose was suboptimal in both the arms (30–40 Gy only) and a subset of the so-called conventional fractionation group received a somewhat unconventional dose/fraction (1.43 Gy/fraction).

In the succeeding years Payne [27] et al. randomized 157 patients of GBM to either conventional fractionation (n = 79) or AHF-RT (n = 78). All patients received CCNU (lomustine) along with radiation. Conventional radiation was delivered to partial brain to a dose of 50 Gy/25 fractions/5 weeks, once daily. AHF-RT was delivered using 1 Gy/fraction, 4 fractions per day at a 3–3.5 hour interfraction interval to a TTD of 36–40 Gy in 2 weeks. The median survival was 10 months vs. 10.6 months for conventional vs. accelerated RT (non-significant).

Shin [28] and colleagues in a similar study design randomized 34 patients to conventional fractionation to a dose of 50 Gy/25 fractions/5 weeks. Thirty-five patients were randomized to the AHF-RT arm which was delivered with 0.89 Gy/fraction, 3 fractions daily to a total dose of 50 Gy in 4 weeks. All the 69 patients received carmustine. The median survival was slightly better in the accelerated arm (13 months) as compared with the conventional arm (9 months), although it did not reach statistical significance because of the small numbers.

To confirm the trend seen in their previous trial, Shin [29] et al. initiated a larger trial of accelerated RT. A total of 124 patients with malignant glioma were randomized to either conventional fractionated RT (40 Gy/20 fractions in 4 weeks to the whole brain with 2 Gy /fraction, followed by a local tumor boost of 20 Gy/10 fractions/2 weeks); or accelerated RT whereby the patients received 0.89 Gy/fraction; 3 fractions/day as whole-brain radiotherapy (WBRT) to a dose of 50.7 Gy/54 fractions in 3.5 weeks followed by a local tumor boost of 10 Gy/5 fractions in 1 week; or to accelerated RT as above plus misonidazole 1.25 gm/m^2 thrice weekly during the first three weeks of radiotherapy. The median survival was 27; 39; and 49 weeks and the 1-year survival probability was 20%; 41%; and 45% respectively for the three randomized arms (which was statistically significant for accelerated RT vs. conventional fractionation, $p < 0.001$). The addition of misonidazole did not alter the survival significantly as compared with accelerated RT alone. From 1984, the authors stopped accrual to the conventional and the AHF-RT plus misonidazole arms, and subsequently all eligible patients were being randomized [30] to AHF-RT as above or high-dose AHF-RT (71.2 Gy/80 fractions/5.5 weeks using 3 fraction daily of 0.89 Gy each).

A phase II randomized trial comparing accelerated radiation with conventional RT was also reported by Ludgate [31] and colleagues. AHF-RT was delivered using 0.76 Gy/fraction, 3 fractions per day to a TTD of 57.6 Gy in 5 weeks (n = 42). Conventional fractionation was delivered to 34 patients to a dose

of 50 Gy/25 fractions/5 weeks. The median survival was 11.5 months in the accelerated arm and although numerically superior to the 8 months' median survival in the conventional arm, did not reach statistical significance, once again possibly due to small numbers in each arm.

The largest phase III randomized trial by Horiot et al. [32] (EORTC 22803) compared conventional fractionation with accelerated fractionation with or without misonidazole. Conventional fractionation was delivered to partial brain to a total dose of 60 Gy/30 fractions over 6 weeks. Accelerated RT was delivered as split course therapy: 30 Gy/5 fractions/ 1week; 3 fractions a day of 2 Gy each at a 4-hour interfraction interval followed by a 2-week rest and then another 30 Gy/5 fractions/1 week; 3 fractions per day for an OTT of 4 weeks. In the third arm misonidazole was also added to the accelerated RT. In all, 340 patients were entered into the study. The median survival was 47 weeks and was remarkably similar in all three arms. The overall survival (OS) in the accelerated arm was 14% and 4% at 2 and 3 years respectively.

The most recent of these was a phase III randomized trial [33] of AHF-RT with or without difluromethyornithine (DMFO) vs. conventionally fractionated RT with or without DMFO for GBM. Here, 231 adults with a histological diagnosis of GBM following surgery were randomized to one of the four treatment arms: Arm A—AHF-RT alone using 2 fractions a day of 1.6 Gy each to a TTD of 70.4 Gy in 44 fractions; Arm B—AHF-RT as above with DMFO 1.8 gm/m^2 orally every 8 hourly; Arm C—conventionally fractionated RT 59.4 Gy/33 fractions/6.5 weeks; or Arm D—conventional RT as in Arm C plus DMFO as given in Arm B. The median OS and PFS were 40 & 19 weeks; 42 & 22 weeks; 37 & 16 weeks; and 44 & 19 weeks for Arms A; B; C; and D respectively, which was not significantly different in any of the four randomized arms. On comparing the two arms containing DMFO, there was no significant difference in the OS (37 weeks vs. 42 weeks) or PFS. Similarly comparison of standard conventional fractionation with the AHF-RT arms showed no difference in the OS (42 weeks vs. 41 weeks) or the PFS. The authors concluded that there was no benefit of DMFO as a radiosensitizer and that standard conventional fractionation remains the treatment of choice for newly diagnosed patients with GBM.

Randomized trial of hyperfractionated RT vs. accelerated radiation

Only one randomized controlled trial has compared hyperfractionated radiotherapy with accelerated radiation. The RTOG 83-02 [34] randomized 786 patients with newly diagnosed malignant gliomas to receive partial brain irradiation, utilizing either Hyperfractionation (1.2 Gy twice daily to various dose levels 64.8 Gy, 72 Gy, 76.8 Gy, or 81.6 Gy) or AHF (1.6 Gy twice daily to doses of 48 Gy or 54.4 Gy in 2½–3 weeks. All patients received carmustine. There was no significant difference between the treatment arms with regards to the median survival, which varied between 10.8 and 12.7 months for all patients. On subset analysis patients of AA did not benefit from the increase in total dose by hyperfractionation (HF), but GBM patients showed significantly superior survival ($p = 0.04$) with the higher total doses in the HF arm (median survival of 11.6 months) as compared with the lower total doses in the AHF arm (median survival of 10.2 months), thereby allowing the authors to conclude that there is scope for dose escalation in GBM.

Studies using predominantly hypofractionated RT

Trials using hypofractionated radiotherapy alone

All prospective non-randomized trials [35–46] using a high dose/fraction alone in malignant gliomas are summarized in Table III. The majority of these were phase I or phase II trials with modest numbers and varying dose schedules. The median dose per fraction was 3.5 Gy (range 2–7 Gy/fraction) and the median number of fractions employed was 10 (range 4–17 fractions). Amongst these only one trial, by Maarten [45] et al., prospectively compared hypofractionated radiation with conventional fractionation and no significant differences were found between the two in terms of palliative effect as well as survival. Two other trials [42,46] compared hypofractionated RT with matched historical controls from previous MRC cohorts treated with conventional fractionation (60 Gy/30 fractions). Although the median survival of patients treated with hypofractionated RT was lesser (by 2.5–4.5 months) than matched controls, the improvement in QOL was reasonably comparable.

Randomized trial of hypofractionated RT

There are three prospective randomized trials evaluating the role of hypofractionated radiotherapy in malignant gliomas. In the first of these Glinski [47] randomized 44 patients with GBM and 64 patients with AA to receive either conventionally fractionated radiotherapy or hypofractionated radiotherapy. Conventional radiotherapy was delivered to the whole brain to a dose of 50 Gy/25 fractions over 5 weeks followed by a coned down field for a tumor-bed

Table III. Prospective trials using hypofractionated RT in malignant gliomas.

Author (ref)	No of pts (n)	TTD (Gy)	No of fx	Dose/fx (Gy)	OTT (wk)	MS (mth)	1-yr survival	Remarks
Hinkelbein (35)	70	31.5–38.5 Gy	9–11 #	3.5 Gy	2 wk	8 mth	NA	–
Mercial Vega (36)	92	51 Gy	17 #	3 Gy	5 wk	12.5 mth	NA	–
Tamura (37)	24	50 Gy	10 #	5 Gy	5 wk	NA	63%	Comparable to conv #
	26	50 Gy	25 #	2 Gy	5 wk	NA	65%	
Bauman (38)	29	30 Gy	10 #	3 Gy	2 wk	6 mth	NA	Inferior to radical RT
Thomas (39)	38	30 Gy	6 #	5 Gy	2 wk	6 mth	NA	Barthels index maintained
Slotman (40)	30	42 Gy	14 #	3 Gy	2 wk	8.5 mth	NA	–
Hoegler (41)	25	37.5 Gy	15 #	2.5 Gy	3 wk	8 mth	NA	–
Ford (42)	32	36 Gy	12 #	3 Gy	2.5 wk	4 mth	NA	Similar to controls
Lang (43)	38	42 Gy	12 #	3.5 Gy	2.5 wk	10.5 mth	34%	–
Jeremic (44)	47	45 Gy	15 #	3 Gy	2.5 wk	9 mth	39%	–
Maarten (45)	155	66 Gy	33 #	2 Gy	6.5 wk	7 mth	NA	No difference in 3 arms
		40 Gy	8 #	5 Gy	17 day	5.6 mth		
		28 Gy	4 #	7 Gy	7–11 days	6.6 mth		
McAleese (46)	92[1]	30 Gy	6 #	5 Gy	2 wk	5 mth	12%	Survival disadvantage of 2.5–4.5 mth with hypoRT
	92[2]	60 Gy	30 #	2 Gy	6 wk	8 mth	19%	

[1]Includes 38 patients from the series of Thomas. [2]All patients were matched controls.

boost of 10 Gy in 5 fractions over 1 week for a TTD of 60 Gy in 30 fractions over 6 weeks. Hypofractionated radiotherapy was delivered in three sessions, each separated by one month. The first two sessions consisted of WBRT each to a dose of 20 Gy in 5 fractions over 1 week. This was followed by final coned-down boost of 10 Gy in 5 fractions over 1 week as in the conventional regimen. In the preliminary report, the 2-year survival for patients with AA was 22% and 18% for conventional and hypofractionated radiation respectively (statistically not significant). Patients with GBM, however, did much better with hypofractionated radiotherapy with a 2-year survival of 23% vs. 10% in the hypofractionation vs. conventional radiation arm (statistically significant, $p = 0.05$).

In another trial [48], patients with poor prognosis high-grade gliomas were randomized postoperatively to receive either conventionally fractionated radiotherapy (local field irradiation to a dose of 60 Gy/30 fractions/6 weeks, $n = 36$) or hypofractionated radiotherapy (to the whole brain to a dose of 35 Gy/10 fractions/2 weeks, $n = 32$). The estimated median survival for all patients was 9.6 months. It was 10.3 months in the 60 Gy arm as compared with 8.7 months in the 35 Gy arm ($p = 0.37$, non-significant). No formal QOL comparison was possible as fewer than 30% of patients could complete the requisite form on follow-up.

In the most recent trial [49], 100 patients with GBM aged 60 years or more were randomly assigned to conventional RT (60 Gy/30 fractions/6 weeks, $n = 51$) or short course RT (40 Gy/15 fractions/3 weeks, $n = 49$). The median overall survival was 5.1 months for conventional fractionation vs. 5.6 months for short course RT ($p = 0.57$). There were no differences in the performance scores between the two groups. However, significantly fewer patients (23% vs. 49%, $p = 0.02$) required an increase in the post-RT steroid dosage in the short course RT arm prompting the investigators to conclude that an abbreviated course of RT seems to be a reasonable option for older patients with GBM. Low completion rates of detailed health-related questionnaires precluded any meaningful objective comparison of QOL, reflecting the challenges of administering such exhaustive QOL tools in such sick patients.

Discussion

There are conflicting data in the literature regarding the benefit of accelerated radiation in poor prognosis malignant gliomas. Most of the non-randomized studies of accelerated radiotherapy (see Table I) have shown that survival and functional outcome are comparable to conventional radiotherapy. The seven randomized studies (Table II) however are not consistent with each other, with the four larger trials [26,27,32,33] reporting no benefit and the two smaller ones [28,31] showing a trend towards improved survival with acceleration over conventional fractionation. Only one study, by Shin et al. [29] reported a survival benefit with accelerated RT. However, the number of patients in their study was small (124 patients only) and only the preliminary results were published. The only trial [34] compar-

ing accelerated RT with hyperfractionation was also negative in the sense that there was no difference between the treatment arms with regards to the median survival, although GBM patients did slightly better with higher dose hyperfractionation. The North Central Cancer Treatment Group (NCCTG) have recently closed accrual to their trial (NCCTG 93-72-52), which is a randomized trial of BCNU alone vs. BCNU/cisplatin and of standard vs. accelerated RT for grade IV gliomas, and their results are eagerly awaited.

Despite three decades of experience, accelerated RT still remains investigational in poor prognosis malignant gliomas and has not gained widespread acceptance. The primary reason for this could be lack of properly designed randomized trials. Although there are several existing randomized trials, they have used varied forms of acceleration with a wide variation in the dose per fraction, number of fractions per day and the total dose delivered. Second, the existing trials—despite moderately large numbers— have not been able to prove any survival benefit, and have included chemotherapy and sensitizers as a confounding factor. Third, although the OTT is somewhat reduced (by 2 weeks on average), this reduction is neither very substantial nor very appealing from the point of view of the patients or their caregivers. Finally, multiple daily fractions would necessitate hospitalization with its attendant socioeconomic and medical implications.

On the other hand, most of the non-randomized studies utilizing a high dose per fraction (see Table III) have also shown that it is comparable to conventional fractionation in malignant gliomas in terms of palliative effect and survival. Only one randomized trial [47] comparing conventional radiation with hypofractionation reported a small but significant survival benefit in patients with GBM but not in AA. However, since this was a preliminary report and there were a limited number of patients in the study (108 patients only), which was not restricted to the poor prognosis subset, no definitive conclusions can be drawn from it. The other randomized trial [48], although restricted to the poor prognosis subset, had to be closed early due to poor accrual and did not demonstrate any survival benefit with conventional fractionation. The median survival and 1-year survival in the Cross Cancer Institute trial [49] was much poorer than even the less favorable subgroup patients from the RTOG database. That this patient population was inherently poor in prognostic terms in terms of age, performance status, and extent of resection may partly explain this difference. Nonetheless a consensus seems to emerge that such a scheme of conformal hypofractionated radiotherapy is feasible, well tolerated and provides equal palliation without compromising on efficacy. The concern for late neurological sequelae in this poor prognosis subset in uncalled for because the expected survival is short. Also, since the OTT is substantially reduced, an increase in therapy-free survival is a welcome bonus. Most importantly, hypofractionated RT would entail less frequent visits to the hospital, which could be of immense value in improving the QOL of these deeply distressed patients and their caregivers. The results of two recently reported phase II trials of hypofractionated Intensity Modulated Radiation Therapy (IMRT) are comparable with conventional fractionation and should provide further impetus to this form of treatment [50,51]. Despite the available evidence in the last three decades hypofractionated radiotherapy is still not accepted as a standard by the oncologic fraternity and remains investigational. Again, the primary reason for this could be a paucity of properly designed prospective randomized trials in this subset, because most of these elderly poor performance status patients are either treated on physician preferences without much scientific evidence or excluded from trial settings. The second reason could be that the existing trials have relatively small numbers, diverse fractionation schedules and conflicting co-variables such as chemotherapy or sensitizers.

Poor prognosis malignant glioma still remains one of the most devastating diseases for the patient and his/her caregiver and the most challenging for his treating physician. No successful treatment has emerged nor is it on the horizon for this largely incurable malady. Patients continue to suffer from symptoms that profoundly affect their QOL such as neurological deficits (hemiplegia, aphasia), cognitive dysfunction, personality changes, and psychosocial ostracization. There is an appalling paucity of data on QOL issues in primary brain cancers, including poor prognosis malignant gliomas [52]. The issue is confounded by the methodological limitations of clinical trial designs, lack of consensus on the appropriate tools to accurately measure QOL in a specific patient population, timescale of measurements, and reporting of QOL outcomes [53]. It is imperative that QOL issues be considered integral to the management of these cancers and that all future trials on malignant gliomas include QOL assessment as an independent outcome measure. QOL assessment is even more relevant when survival is limited and other issues of the patient's life are more important. It is more likely to have implications for clinical decision-making and impact on the choice of fractionation for this patient population. Such patients may gain clinically significant benefit from

interventions based on robust QOL outcomes alone without the advantage of a survival benefit.

Conclusion

There exist no class solutions as far as fractionation in poor prognosis malignant gliomas is concerned. Although both accelerated RT and hypofractionated RT compare equally well with conventional fractionation in terms of survival, palliation, quality of life, and morbidity, a randomized trial comparing both these forms of altered fractionation may help in the search for an answer to this elusive question. In the good prognosis gliomas, a boost to the tumor bed using interstitial brachytherapy or stereotactic radiosurgery has been explored as a means of dose escalation for better local control. Their place in the poor prognosis subset remains to be defined. However, hypofractionated stereotactic radiotherapy or hypofractionated IMRT may be where the answer lies. Nevertheless, one has to admit that modifying the fractionation does add some degree of complexity to what essentially remains a palliative treatment regimen. Its rationale needs to be re-examined from the perspective of its impact on QOL, patient and caregiver preferences, local logistics of the treating institution, and health-economic considerations.

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