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REVIEW ARTICLE

# Hypofractionated radiotherapy for glioblastoma: strategy for poor-risk patients or hope for the future?

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**ABSTRACT.** The prognosis of patients with glioblastoma (GBM) remains poor, and the use of hyperfractionation or dose escalation beyond 60 Gy has not conferred any survival benefit. More recently, hypofractionated radiotherapy (HFRT) has been employed as a novel approach for achieving dose escalation, with interesting results. We present here a systematic overview of the role and development of HFRT as a possible therapeutic strategy in patients with GBM. We searched the PubMed database for studies published since 1990 that reported on the tolerance, safety and survival outcomes after HFRT. These studies reported on the paradox of improved survival in patients developing central radionecrosis within the high-dose volume. Most series reported no significant increase in early or late toxicity, except for one study that reported visual loss in one patient at 7 months after treatment. More recently, studies of HFRT combined with concurrent temozolomide (TMZ) reported a trend towards improved survival compared with historical controls, with a few studies reporting a median survival of approximately 20 months. The interpretation of data from the above studies is limited by the heterogeneities of patient population and the significant variation in the range of employed dose schedules. However, high-dose HFRT using intensity-modulated radiotherapy appears to be a safe and feasible therapeutic option. There is a suggestion of improved outcomes on combining HFRT with TMZ, which warrants further investigation in a randomised trial.

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The prognosis of patients with glioblastoma (GBM) is universally poor, with few long-term survivors [1]. The publication of the pivotal European Organisation for Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada Clinical Trials Group Phase III randomised trial in 2005 established the role of post-operative radiotherapy (RT) combined with concurrent and adjuvant temozolomide (TMZ) as the standard of care in these patients. However, the overall outcome remains poor, with a median survival (MS) of approximately 12 and 14.5 months after adjuvant radiation and TMZ-based chemoradiotherapy (CRT), respectively.

The EORTC trial explored the use of concurrent TMZ with a conventional radiation schedule of 60 Gy in 2.0 Gy per fraction based on results from previous dose-exploratory studies [2, 3]. However, the outcome following the use of protracted radiation schedules can be compromised from tumour repopulation in tumours such as GBM with rapid doubling time [4]. Approximately 12% to 37.5% of patients may clinically progress at the end of a conventionally fractionated radiation schedule [5]. The age, performance status and extent of surgery are important prognostic factors that formed the basis for the development of the recursive partitioning analysis (RPA) prognostic categorisation by the Radiation Therapy Oncology Group (RTOG). Patients falling into higher RPA categories have poor prognosis and often progress through conventional protracted radiation schedules.

Hypofractionation has the dual advantage of achieving increased cell kill from a higher dose per fraction and reducing the effect from accelerated tumour cell repopulation by shortening the overall treatment time. However, the potential advantage may be offset by increased toxicity in the late-responding neural tissues. The initial exploration of hypofractionated radiotherapy (HFRT) schedules was purely driven from the convenience perspective of reducing the overall treatment time in the poor-prognosis subgroup of patients. Many of these initial studies reported equivalent outcomes to conventional fractionation, despite the use of a lower total radiation dose. More recently, investigators have attempted delivering radical doses of HFRT using intensity-modulated RT (IMRT). These studies have particularly focused on escalating the dose in the immediate vicinity of the enhancing tumour and post-operative surgical cavity, and reported reasonable outcomes with acceptable levels of toxicity.

This article presents a systematic overview on the role of HFRT in patients with GBM, and, in particular,

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the delivery of HFRT within the realms of modern RT planning and IMRT.

## Methods and materials

We searched the PubMed and MEDLINE databases using one or more of the following keywords: glioblastoma, radiotherapy, hypofractionated radiotherapy. The following limits were applied:

(1) date: published since 1990
(2) language: English
(3) species: human.

We aimed to identify studies that had reported on the outcomes after partial-brain HFRT—safety, toxicity and survival—in newly diagnosed patients with GBM. In particular, we searched for studies that had combined HFRT with concurrent or adjuvant TMZ. We excluded studies that had used HFRT for recurrent disease or those employing hypofractionated stereotactic radiosurgery.

For the purpose of the review, we discuss the studies according to the level of dose intensity using a simplistic linear-quadratic (LQ) model for tumour control probability. The biological effective dose (BED) is a measure of effect in units of $Gy_x$, where the suffix $x$ indicates the value of $\alpha/\beta$ assumed in the calculation. The tumour BED takes into account the repopulation factor and is defined by the following equation:

$$nd(1+d/\alpha/\beta)-\mathrm{T}0.693/\alpha T_{\mathrm{eff}} \quad (1)$$

where $n$ and $d$ represent the number and size of the dose fractions, respectively, and $\alpha$ and $\beta$ are the respective LQ radiosensitivity coefficients of the tumour tissue, $T$ is the treatment time, and $T_{\mathrm{eff}}$ represents the effective doubling time. There are few reliable estimates of tumour doubling time, and these have ranged from 3 to 39.5 days [6–11]. For the calculation of tumour BED we employed the $T_{\mathrm{eff}}$ value of 22 days, which represents an average of previously reported estimates. In addition, we employed an $\alpha$ estimate of $0.26\,\mathrm{Gy}^{-1}$ and an $\alpha/\beta$ ratio of 8 Gy based on the average values of previously reported estimates of alpha and beta from other studies [4, 8, 12–15] The tumour BED from conventional 60 Gy in 30 fractions is approximately $69.91\,\mathrm{Gy}_8$ using the above calculation. Therefore, for the purpose of the review we discuss the studies based on the threshold of tumour BED of $70\,\mathrm{Gy}_8$, which represents a close approximation of the biological dose delivered with conventional fractionation. The biological equivalent dose of late-responding tissues to conventional fractionation was estimated using the following equation:

$$\mathrm{BED\text{–}late}=D1(d1+\alpha/\beta/d2+\alpha/\beta) \quad (2)$$

where $D1$ and $d1$ represent the total and dose per fraction from the HFRT schedule, respectively, $d2$ is the conventional fraction size (2 Gy), and $\alpha/\beta$ represents the LQ coefficients of late-responding tissues (2 Gy).

The original search revealed 2283 citations, from which 21 papers were selected for further discussion. We identified five retrospective, four prospective (single-arm) and three randomised studies of HFRT that employed a tumour BEDs dose of less than $70\,\mathrm{Gy}_8$. In addition, we identified four single-arm prospective series of high-dose HFRT that delivered tumour BEDs of more than $70\,\mathrm{Gy}_8$ using IMRT. Furthermore, we identified four prospective (single-arm) and one retrospective series of HFRT combined with TMZ.

## Results

### *Hypofractionated radiotherapy with tumour biological effective dose of less than $70\,\mathrm{Gy}_8$*

Table 1 summarises characteristics from published studies of HFRT with tumour BED of less than $70\,\mathrm{Gy}_8$. Thomas et al [16] reported on a retrospective series from the Royal Marsden Hospital, Sutton, UK, of 38 patients with poor prognostic features who were treated with 30 Gy in six fractions over 2 weeks. The planning target volume (PTV) was defined by the enhancing tumour and a 2 cm margin. The MS was 6 months with a 1 year survival rate of 23% without any significant toxicity [16]. In 2003, the same group reported on an expanded retrospective cohort of 92 poor-prognosis patients and reported a MS of 5 months with a 1 year survival rate of 12%, which was inferior to matched controls treated with conventionally fractionated RT (60 Gy), 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 [17].

In another retrospective series from the MD Anderson Cancer Center, Houston, TX [18], 59 patients with GBM were treated with a HFRT regimen of 50 Gy in 20 fractions. More than two-thirds of patients were older than 60 years of age and 35% of patients had Karnofsky performance status (KPS) of less than 70. 44 patients had undergone surgical debulking. The study employed a two-phase technique, with 40 Gy in 16 fractions delivered in the first phase to enhancing tumour plus a 3 cm margin, and a second phase (10 Gy in four fractions) with a reduced margin of 1 cm. The study reported an MS of 7 months, similar to the RTOG data, when taking into account the RPA class. No significant acute toxicity was observed, with most patients completing treatment. However, the study reported two confirmed and one possible case of radiation necrosis [18].

Lutterbach and Ostertag [19] reported on a German retrospective series of 96 GBM patients older than 60 years of age who received 42 Gy in 12 fractions ($n$=50) or conventional 60 Gy in 30 fractions ($n$=46). The median age was 67 years, with 60% of the patients having a KPS of more than 70, and 59% had undergone gross total resection (GTR) or subtotal resection (STR). The median, 1 and 2 year overall survival (OS) was 7.3 months, 60% and 26% in the hypofractionated group, compared with 5.6 months, 49% and 18% in the conventionally fractionated group, respectively. No significant long-term toxicity was observed with HFRT [19].

In a retrospective series from The Johns Hopkins University, Baltimore, MD [20], 219 patients with malignant glioma (GBM=185) were treated with a hypofractionated split-course RT regimen (SHORT)

**Table 1.** Published studies of hypofractionated radiotherapy (HFRT) with tumour biological effective dose (BED) of <70 $Gy_8$

| Authors/study | RT planning | HFRT protocol | BED ($Gy_8$) tumour | BED ($Gy_2$) late effects | Outcome |
|---|---|---|---|---|---|
| Thomas et al [16]<br>Retrospective<br>*n*=38 | Enhancing tumour with 2 cm margin | 30 Gy in 6 fractions over 2 weeks | 47 | 52.5 | MS=6 months<br>1 year survival=23%<br>No significant toxicity |
| McAleese et al [17]<br>Retrospective<br>*n*=92 | Enhancing tumour with 2 cm margin | 30 Gy in 6 fractions over 2 weeks | 47 | 52.5 | MS=5 months<br>1 year survival=12%<br>No significant toxicity |
| Chang et al (2003) [18]<br>Retrospective<br>*n*=59 | Enhancing tumour plus 3 cm margin—Phase 1<br>Enhancing tumour plus 1 cm margin—Phase 2 | 40 Gy in 16 fractions—Phase 1<br>10 Gy in 4 fractions—Phase 2 | 62.25 | 56.25 | MS=7 months<br>(poor prognosis sub-group)<br>No significant toxicity |
| Lutterbach et al [19]<br>Retrospective<br>*n*=50 | Single phase | 42 Gy in 12 fractions | 58.5 | 57.75 | MS=7.3 months<br>2 year survival=26%<br>No significant toxicity |
| Kleinberg et al [20]<br>Retrospective<br>*n*=219 (GBM=185) | Shrinking field technique | 30 Gy in 10 fractions—Phase 1<br>21 Gy in 7 fractions—Phase 2 | 67.5 | 63.75 | MS=13, 8, 5 months in RPA IV, V, and VI, respectively<br>No significant toxicity |
| Ford et al [22]<br>Prospective<br>*n*=32 | Enhancing tumour and oedema with 2 cm margin | 36 Gy in 12 fractions | 47.5 | 45 | MS=16 weeks<br>Poor prognosis group<br>No significant toxicity |
| Slotman et al [21]<br>Prospective<br>*n*=30 | Enhancing tumour and oedema plus 3 cm margin—Phase 1<br>Enhancing tumour plus 1.5 cm margin—Phase 2 | 30 Gy in 10 fractions—Phase 1<br>12 Gy in 4 fractions—Phase 2 | 55.5 | 52.5 | MS=9 months<br>MS=12 months in good-prognosis patients<br>No significant toxicity |
| Sayin et al [24]<br>Prospective<br>*n*=31 | Single phase | 45 Gy in 15 fractions after GTR (*n*=10)<br>54 Gy in 18 fractions after STR (*n*=21) | 59<br>71 | 56.25<br>67.5 | MS=8 months<br>1 year survival=40%<br>No significant toxicity<br>No significant toxicity |
| Arslan et al [23]<br>Prospective<br>*n*=20 | Shrinking-field technique<br>12 fractions—Phase 1<br>3 fractions—Phase | 50 Gy in 15 fractions | 68 | 66.66 | MS=12 months<br>1 year survival=50%<br>No significant toxicity |
| Glinski et al [25]<br>RCT<br>*n*=108 | WBRT—Phases 1 and 2<br>Enhancing tumour plus 2–3 cm margin—Phase 3 | 20 Gy in 5 fractions—Phase 1<br>20 Gy in 5 fractions—Phase 2<br>10 Gy in 5 fractions—Phase 3<br>(4 week gap between each phase) | 65 | 70 | 2 year survival of 23%<br>in HFRT arm compared with 10% with conventional RT<br>No significant toxicity |
| Roa et al [26]<br>RCT<br>*n*=100 | Enhancing tumour and oedema plus 2.5 cm margin | 40 Gy in 15 fractions compared with 60 Gy in 30 fractions | 50.5 | 46.7 | MS of 5.6 months with HFRT compared with 5.1 months with conventional RT<br>MS=8.8, 6.9, and 4.8 months in RPA IV, V and VI, respectively<br>No significant toxicity |
| Hulshof et al [27]<br>RCT<br>*n*=155 | Enhancing tumour plus 1.5 cm margin<br>Two dose levels in experimental arm | 40 Gy in 5 fractions—3 fractions per week<br>28 Gy in 4 fractions—2 to 3 fractions per week | 78<br>51 | 100<br>63 | MS of 5.6 months and<br>6.6 months in the 40 Gy and 28 Gy arms, respectively.<br>No significant toxicity |

GBM, glioblastoma; GTR, gross tumour resection; MS, median survival; RCT, randomised controlled trial; RPA, recursive partitioning analysis; RT, radiotherapy; STR, subtotal resection; WBRT, whole-brain RT.

The dose threshold of 70 $Gy_8$ represents a close approximation of tumour BED from conventional fractionation (60 Gy in 30 fractions) based on linear-quadratic estimates. The BED of late-responding tissues represents the biological-equivalent dose compared with the conventional fraction size (2 Gy) and is based on the presumed $\alpha/\beta$ estimate of 2 Gy.

using a shrinking-field technique with initial phase of 30 Gy in 10 fractions delivered to a larger area of brain (51% received whole-brain RT) followed by reduced 21 Gy in seven fractions to a reduced volume. The series included a good-prognosis subgroup with 33% of patients less than 50 years of age; 72% had a KPS of more than 70 (RTOG I–III=46). The trial reported an MS of 68, 57, 22, 13, 8 and 5 months, and a 2-year survival of 64%, 67%, 45%, 8%, 3% and 3%, in RTOG groups I–VI, respectively. In the opinion of the authors, the above results were similar to those achieved by employing more aggressive treatment protocols. No significant treatment-related toxicity was observed and the authors recommended the SHORT regimen as an appropriate treatment option for most patients with malignant glioma [20].

Slotman et al [21] reported on a small prospective Dutch series of 30 patients with GBM who were treated with HFRT regimen of 42 Gy in 14 fractions. The mean age of patients was 57 years and half the patients had a KPS of 80–100. 20 patients underwent good surgical debulking with removal of more than 75% of the primary tumour. The study employed a two-phase technique, with the first phase treating the enhancing tumour including oedema with a margin of 3 cm to a dose of 30 Gy in 10 fractions. The second phase involved a further 12 Gy in four fractions delivered to reduced volume with a margin of 1.5 cm. The study reported an overall MS of 36 weeks, which increased to 42 weeks in patients with near-total resection. Patients with good prognostic features (age <50 years; KPS >70; good surgical debulking) had an MS of 50 weeks. No significant acute or delayed toxicity was reported [21].

Ford et al [22] reported on a small UK prospective series of 32 patients with high-grade glioma and poor prognostic features [Medical Research Council (MRC) prognostic score >25] treated at the Addenbrookes Hospital Cambridge, UK, with a dose of 36 Gy in 12 fractions to the tumour and surrounding oedema with a 2 cm margin. 28 patients completed treatment as planned and the MS for the whole group was 16 weeks, with 7 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 [22].

Arslan et al [23] reported on a prospective series of 20 patients with GBM who were treated with HFRT using 50 Gy in 15 fractions over 5 weeks. All patients underwent total ($n$=10) or partial ($n$=10) tumour excision, and treatment was delivered 3 days per week using a shrinking-field technique, with a first phase of 12 fractions and a second phase of 3 fractions. The study reported a 1 year survival of 50% and an MS of 12 months. Treatment was well tolerated, with no observed acute toxicity, and one patient developed necrosis within the high-dose volume. The use of HFRT was associated with non-significant improvement in outcome compared with a historical control group treated with conventional RT [23].

Sayin et al [24] reported on a prospective series of 31 patients with malignant glioma who were treated with HFRT using 45 Gy in 15 fractions after GTR ($n$=10) or a dose of 54 Gy in 18 fractions after STR ($n$=20). The MS was 8 months with an actuarial 1 year survival of 40%. No grade 3–4 acute or late neurotoxicity was observed. The tolerance of patients to HFRT was no different from that of conventional RT [24].

In a Polish series from the Maria Slodowska Curie Memorial Center, Krakow, Poland, 108 patients with malignant glioma (GBM=44; anaplastic astrocytoma =64) were randomised to conventional or hypofractionated RT. The study employed an atypical protocol, with the conventional arm receiving whole-brain RT (50 Gy in 25 fractions) in the first phase, followed by a second phase (10 Gy in 5 fractions) including the enhancing tumour plus a 2–3 cm margin. By comparison, patients in the HFRT group were treated with two different schedules of 20 Gy in five fractions to whole brain followed by final phase of 10 Gy in five fractions including the enhancing tumour plus a 2–3 cm margin, with a 4-week elective gap between each treatment phase. No significant toxicities were observed and despite the prolonged overall treatment time patients treated with HFRT had a significant 2 year improvement in survival of 23%, compared with 10% in the conventional fractionation arm [25].

Roa et al [26] randomly assigned 100 GBM patients aged 60 years or older to conventional RT (60 Gy in 30 fractions) or HFRT (40 Gy in 15 fractions) to the partial brain. The PTV included the enhancing primary tumour and surrounding oedema with a 2.5 cm margin. The MS was 5.1 months in the conventional RT group and 5.6 months in the HFRT group ($p$=0.57). MS times for patients belonging to RPA Classes IV, V, and VI were 8.8, 6.9 and 4.8 months, respectively [26]. In another prospective study from Netherlands, Hulshof et al [27] treated 155 patients with GBM with 3 different partial-brain RT regimens (66 Gy in 33 fractions *vs* 40 Gy in 5 fractions *vs* 28 Gy in 4 fractions). The PTV included the enhancing tumour with a 1.5 cm margin. Patients who were 60 years or older, or with a poor performance status, were treated with one of the hypofractionated regimens. The MS was 5.6 and 6.6 months for the 40 Gy and 28 Gy regimens, respectively, comparing favourably with patients treated with the 66 Gy (conventional) regimen [27].

### *Hypofractionated radiotherapy with tumour biological effective dose of more than 70 $Gy_8$*

Table 2 summarises characteristics from published studies of IMRT-based high-dose HFRT with a tumour BED of more than 70 $Gy_8$. Floyd et al [28] reported on one of the earliest Phase 1 studies of dose-intense HFRT in 18 patients with GBM using IMRT-based planning. A dose of 50 Gy was delivered in 5 Gy daily fractions over 2 weeks to enhancing primary disease, residual tumour or surgical cavity, depending on the extent of resection, and 30 Gy was simultaneously prescribed in 3 Gy daily fractions to surrounding oedema. All patients had an initial KPS of 70 and were grouped as follows: RPA Class III ($n$=3), IV ($n$=11) or V ($n$=4). No significant acute toxicity was reported. However, three patients underwent a second craniotomy and tissue excision, with pathological confirmation of cerebral necrosis. In all cases, necrosis, as identified on MRI, appeared to be within the high-dose region specified during treatment

**Table 2.** Published studies of intensity modulated radiotherapy (IMRT)-based high-dose hypofractionated radiotherapy (HFRT) with tumour biological effective dose (BED) of >70 $Gy_8$

| Authors/study | RT planning | HFRT protocol | BED ($Gy_8$) tumour | BED ($Gy_2$) late effects | Outcome |
|---|---|---|---|---|---|
| Floyd et al [28]<br>Prospective<br>$n$=18 | IMRT<br>Enhancing tumour—PTV1<br>Oedema—PTV2 | 50 Gy in 10 fractions—PTV1<br>30 Gy in 10 fractions—PTV2 | 79.5<br><br>39.5 | 87.5 | MS=7 months<br>3 patients who developed radiation necrosis had survival times of 23, 20 and 9 months |
| Sultanem et al [29]<br>Prospective<br>$n$=25 | IMRT<br>Enhancing tumour—PTV1<br>Tumour plus 1.5 cm margin=PTV2 | 60 Gy in 20 fractions—PTV1<br>40 Gy in 20 fractions—PTV2 | 79<br><br>46.5 | 75 | MS=9.5 months<br>(15 patients with RPA V-VI)<br>1 year survival 40%<br>No significant toxicity |
| Iuchi et al [30]<br>Prospective<br>$n$=25 (GBM=23)<br>Phase 1 dose-escalation design | IMRT<br>Enhancing tumour plus 5 mm margin—PTV1<br>Tumour plus 2 cm margin—PTV2<br>Oedema—PTV3 | Treatment delivered in 8 fractions<br>Dose escalation—PTV1<br>DL1=48 Gy<br>DL2=56 Gy<br>DL3=60 Gy<br>DL4=64 Gy<br>DL5=68 Gy<br>PTV2=40 Gy (constant)<br>PTV3=32 Gy (constant) | PTV1<br>DL1=82.5 ($n$=2)<br>DL2=103.5 ($n$=2)<br>DL3=114.5 ($n$=3)<br>DL4=126.5 ($n$=5)<br>DL5=138.5 ($n$=13)<br>PTV2=63.5<br>PTV3=46.5 | PTV1<br>DL1=96 Gy<br>DL2=126 Gy<br>DL3=142.5 Gy<br>DL4=160 Gy<br>DL5=178.5 Gy<br>PTV2=70 Gy<br>PTV3=48 Gy | 1 year and 2 year survival of 71.4% and 55%, respectively<br>3 patients who developed cerebral necrosis had a survival time in excess of 17 months |
| Monjazeb et al [31]<br>Prospective<br>$n$=21 good risk (RPA III-IV) | IMRT<br>Enhancing tumour with 5 mm margin—PTV1<br>Tumour plus oedema plus 1 cm margin—PTV2 | 3 dose levels to PTV1<br>DL1=70 Gy in 28 fractions<br>DL2=75 Gy in 30 fractions<br>DL3=80 Gy in 32 fractions<br>PTV2=50.4 Gy in 28 fractions (constant) | PTV1<br>DL1=87<br>DL2=93<br>DL3=99.5<br>PTV2=57 | PTV1<br>DL1=78.75 Gy<br>DL2=84.50 Gy<br>DL3=90 Gy | MS=13.6 months<br>1 year and 2 year survival of 57% and 19%, respectively |

DL, dose level; GBM, glioblastoma; MS, median survival; PTV, planning target volume; RPA, recursive partitioning analysis; RT, radiotherapy.

The dose threshold of 70 $Gy_8$ represents a close approximation of tumour BED from conventional fractionation (60 Gy in 30 fractions) based on linear-quadratic (LQ) estimates. The BED of late-responding tissues represents the biological-equivalent dose compared with the conventional fraction size (2 Gy) and is based on the presumed $\alpha/\beta$ estimate of 2 Gy, where $\alpha$ and $\beta$ are the respective LQ radiosensitivity coefficients of the tumour tissue. The PTV1 signifies the high-dose region including the enhancing tumour and post-operative surgical cavity with appropriate margins.

planning. Mortality in all cases was the result of tumour recurrence. No mortality occurred as a result of cerebral necrosis from RT [28]. The median OS was 7 months and all recurrences were within 2 cm of the operative bed. Interestingly, the 3 patients with brain necrosis had much improved survival at 23, 20 and 9 months, compared with the rest of the group. The study had originally intended to recruit 78 patients, but closed early because of the unusually high incidence of radiation necrosis. The paradoxical effect of necrosis on survival became obvious only on subsequent analysis.

Sultanem et al [29] reported on a prospective Canadian series of 25 patients from McGill University, Montreal, Canada, which evaluated the use of HFRT using IMRT as adjuvant treatment after surgery in patients with GBM. 6 patients underwent GTR, 11 had STR resection and 8 had biopsy only. Roughly two-thirds of the patients (15 out of 25) had RPA Class V–VI. The study protocol specified a post-operative tumour volume of 110 $cm^3$ or less and excluded patients with tumours within 1.5 cm of critical structures such as the brain stem or optic chiasm. The PTV was defined as the enhancing tumour plus a 1.5 cm margin. The study employed a relatively simplistic forward-planning approach with intensity modulation using a smaller multileaf collimator-defined field covering the gross tumour volume (GTV) superimposed on a larger field covering the PTV, which was delivered using a step-and-shoot dynamic beam delivery. A total dose of 60 Gy in 20 fractions over 4 weeks was prescribed to the isocentre with the 95–100% isodose covering the GTV (60 Gy), and the PTV periphery was included within the 65–70% isodose (40 Gy), leading to a dose gradient through the PTV with full dose delivered adjacent to the GTV. The MS was 9.5 months (range 2.8–22.9 months), and the 1 year OS rate was 40%. No significant toxicity was reported. However, 5 out of 25 patients required an increase in steroid dosage as a result of progressive neurological symptoms, which was due to increased oedema in the 2 patients who underwent imaging. All recurrences were central, with no patient relapsing distantly outside the irradiated volume [29].

Iuchi et al [30] reported on a Phase 1 cohort of 25 patients with high-grade glioma (GBM=23) treated with HFRT using IMRT. Nearly all patients were in the RTOG IV–VI groups ($n$=24), with a median age and KPS of 62 and 70 years, respectively. The tumour volume ranged from 3.9 to 132.5 $cm^3$ and the study protocol involved a three-layered contouring of PTV: PTV1 included GTV (enhancing tumour) with a 5 mm margin; PTV2 included another 15 mm margin surrounding the PTV1; PTV3 was extended to include the peritumoural oedema. Irradiation was performed in eight fractions and the study employed a dose-escalation protocol for PTV1 while maintaining a constant dose for PTV2 (40 Gy) and PTV3 (32 Gy). The dose levels for PTV1 were 48 ($n$=3), 56 ($n$=2), 60 ($n$=3), 64 ($n$=5) and 68 Gy ($n$=13). Dose escalation was associated with an improvement in OS and the study reported 1-year and 2-year OS of 71.4% and 55.4%, respectively, in the IMRT group, which was significantly superior to a parallel cohort of 60 patients treated with conventional RT ($p$=0.043). The study reported an interesting difference in pattern of relapse between patients treated with high-dose HFRT and conventional RT. Two-thirds ($n$=43) of patients treated with conventional external-beam radiotherapy (EBRT) developed local failure. By comparison, only six patients in the HFRT arm developed local failure, but eight patients showed cerebrospinal fluid (CSF) dissemination, which was the commonest cause of death. Radiation necrosis was observed in three patients requiring repeat surgery in the HFRT group, but two patients were still alive at 17 months and the other patient died of CSF dissemination 20 months after treatment [30].

Monjazeb et al [31] reported on a Phase 1 dose-escalation study of HFRT in 21 good-risk (RPA III–IV) patients with GBM (mean age 55 years; KPS >70) with post-operative $T_1$ enhancing tumour measuring <5 cm or a pre-operative $T_1$ enhancing abnormality of <8 cm. 9 patients were RPA Class III and 12 were RPA Class IV. 8 patients underwent GTR, 9 patients underwent STR and 4 patients underwent biopsy only. The study employed a dual-layered approach for volume definition, with PTV1 including a margin of 0.5 cm around the enhancing tumour and PTV2 with a margin of 1 cm around the enhancing tumour and surrounding $T_2$ abnormality (oedema). The PTV2 group was prescribed 50.4 Gy in 28 fractions with a field-in-field concomitant boost of 0.7 Gy to PTV1 (70 Gy in 28 fractions). The study explored dose-escalation Phase 1 design with investigation of three separate dose levels to PTV1 (70 Gy, 75 Gy and 80 Gy), with the dose-escalation schedule involving an extended phase of 2–4 fractions to achieve the appropriate PTV1 dose level. The trial reported no dose-limiting toxicity and no significant increase in late toxicity after HFRT. The MS was 13.6 months, with 1 and 2 year survival rates of 57% and 19%, respectively [31].

### *Hypofractionated radiotherapy combined with temozolomide*

Table 3 summarises characteristics from published studies of HFRT with concurrent and adjuvant TMZ. Minniti et al [32] reported on a prospective series of 43 patients with GBM treated with HFRT followed by adjuvant TMZ. All patients were 70 years of age or older, with a KPS of more than 60, and were treated with 30 Gy in 6 fractions over 2 weeks, followed by up to 12 cycles of adjuvant TMZ. The MS was 9.3 months and the median progression-free survival (PFS) was 6.3 months. The 6 and 12 month survival rates were 86% and 35%, respectively. The regime was well tolerated, with no significant toxicity related to the use of RT and no deleterious effect on quality of life. The authors concluded that HFRT followed by TMZ may provide survival benefit while maintaining a good quality of life in elderly patients with GBM [32].

Chen et al [33] reported on study of HFRT with concurrent and adjuvant TMZ (median cycles=7.5) in 19 patients with GBM. The study employed a PTV1 with a margin of 5 mm around the enhancing tumour and PTV2 with a margin of 5 mm around the enhancing tumour and surrounding $T_2$ abnormality (oedema). The study explored four dose levels to the central tumour area, starting from 60 Gy in 3 Gy per fraction (level 1) to 60 Gy in 6 Gy per fraction (level 4) with the dose per fraction increasing by 1 Gy in each cohort. The total number of fractions decreased from 20 to 10 as the fraction size to the PTV1

**Table 3.** Published studies of high-dose hypofractionated radiotherapy (HFRT) with concurrent and adjuvant temozolomide

| Authors/study | RT planning | HFRT protocol | BED ($Gy_8$) tumour | BED ($Gy_2$) late effects | Outcome |
|---|---|---|---|---|---|
| Chen et al [33]<br>Prospective<br>$n$=19<br>Phase 1 dose-escalation design (3+3) | IMRT<br>Enhancing tumour plus 5 mm margin—PTV1<br>Tumour plus oedema plus 5 mm margin—PTV2 | 4 dose levels<br>PTV1/PTV2/fractions (Gy)<br>60/45/20=DL1<br>60/40.5/15=DL2<br>60/36/12=DL3<br>60/30/10=DL4<br>Concurrent and adjuvant TMZ | 4 dose levels<br>PTV1/PTV2 (Gy)<br>79/54.25=DL1<br>87.5/51.5=DL2<br>95.5/47.5=DL3<br>103.5/39.5=DL3 | 75=DL1<br>90=DL2<br>105=DL3<br>120=DL3 | MS=16.2 months<br>3 patients who developed central necrosis had a MS of 20 months<br>Grade 4 toxicity in one patient with visual loss at 7 months (radiation necrosis and tumour regrowth) |
| Panet Raymond et al [34]<br>Retrospective<br>$n$=35<br>Most patients RPA V–VI ($n$=26) | IMRT<br>Enhancing tumour—PTV1<br>Tumour plus 1.5 cm margin—PTV2 | 60 Gy in 20 fractions—PTV1<br>40 Gy in 20 fractions—PTV2<br>Concurrent and adjuvant TMZ | 79<br>46.5 | 75 | MS of 14.4 months<br>RPA III/IV=17.9 months<br>RPA V/VI=12.9 months<br>No significant toxicity |
| Terasaki et al [35]<br>Prospective<br>$n$=26 | Single-phase enhancing tumour plus 2 cm margin | 45 Gy in 15 fractions with concurrent and adjuvant TMZ | 59.5 | 56.25 | MS of 15.6 months<br>No significant toxicity |
| Morganti et al [36]<br>Prospective<br>$n$=19<br>Phase 1 dose-escalation study | IMRT<br>Tumour plus 1.5 cm margin—PTV1<br>Tumour plus oedema+1.5cm=PTV2<br>IMRT<br>Tumour plus 1.5 cm margin—PTV1<br>Tumour plus oedema+1.5cm=PTV2 | 25 fractions over 5 weeks<br>3 dose-levels for PTV1(Gy)<br>DL1=60<br>DL2=62.5<br>DL3=65<br>PTV2=45 Gy (constant) | PTV1—3 dose levels (Gy)<br>DL1=73.75<br>DL2=77.75<br>DL3=82<br>PTV2=51 | DL1=66<br>DL2=70.5<br>DL3=74.75 | MS of 20 months<br>1 year survival=82%<br>2 year survival=29% |

BED, biological effective dose; DL, dose level; IMRT, intensity-modulated radiotherapy; MS, median survival; PTV, planning target volume; RPA, recursive partitioning analysis; RT, radiotherapy.
The tumour biological effective dose is based on linear-quadratic estimates.
The BED of late-responding tissues represents the biological-equivalent dose compared with the conventional fraction size (2 Gy) and is based on the presumed $\alpha/\beta$ estimate of 2 Gy, where $\alpha$ and $\beta$ are the respective linear-quadratic radiosensitivity coefficients of the tumour tissue.
The PTV1 in IMRT-based planning signifies the high-dose region, including the enhancing tumour and post-operative surgical cavity with appropriate margins.

increased from 3 to 6 Gy. The total dose to the PTV2 was decreased from 45 Gy (2.25 Gy per fraction) in Level 1 to 30 Gy (3 Gy per fraction) in Level 4. In Level 4, the recommended maximal dose to the optic chiasm, optic nerves and the retina of at least one eye was <30 Gy, and to the brain stem was <35 Gy. The study employed a 3+3 Phase 1 design, with three each at Levels 1 and 2, four at Level 3, and six at Level 4. The median age and KPS were 69 years and 80, respectively, and 8 patients underwent GTR, 5 patients underwent STR and 3 patients had biopsy (RPA III=6, IV=8, V=2). The trial reported on acute or late dose level threshold (DLT) at any of the dose levels, except in one patient treated at dose Level 2 who developed visual loss in left eye at 7 months after RT, primarily from radiation-induced late toxicity effect, but there was associated tumour regrowth (see below). The trial reported MS of 16.2 months, with all patients developing central recurrence except two who relapsed at the 30 Gy isodose line. Of the 16, 4 underwent a second craniotomy for radiological progression documented on MRI. The craniotomy showed tumour recurrence in 1 patient (Level 1) and necrosis with minimal residual tumour in the remaining 3. Patients developing radiation necrosis had no significant symptoms and showed an MS of 20.3 months [33].

Panet-Raymond et al [34] reported on a retrospective Canadian series of 35 patients from McGill University who were treated using HFRT with concurrent and adjuvant TMZ. The same group had previously reported on the use of IMRT-based HFRT with a concomitant boost technique using a dose of 60 Gy and 40 Gy in 20 fractions delivered to GTV (PTV1) and PTV2 (1.5 cm margin around GTV), respectively [29]. The median age was 63 years, and 13 patients underwent GTR, 13 patients underwent STR and 9 patients had biopsy alone. Most patients were in RPA Class V ($n$=20), with two in Class III, seven in Class IV, and six in Class VI. The trial did not report any significant acute or late toxicities. The trial reported an overall MS of 14.4 months, which was significantly higher in patients who had debulking surgery (16.1 months) than in those who had biopsy (7.1 months; $p$=0.035). The MS for those with RPA Class III–IV was 17.9 months and for those with Class V–VI it was 12.9 months. As with conventional fractionation, the $O^6$-methylguanine–DNA methyltransferase (MGMT) promoter methylation status was a significant prognostic indicator for MS of (14.4 months for methylated *vs* 8.7 months for unmethylated; $p$=0.049). As with previous studies, most of the radiologically confirmed tumour recurrences (21/23) were central, with only 2 patients developing failure of >2 cm from the initial GTV [34].

Terasaki et al [35] reported on a Japanese prospective series of 26 patients with GBM treated with HFRT and TMZ. Patients received 45 Gy in 15 fractions over 3 weeks with concomitant and adjuvant TMZ, and were treated with standard three-dimensional conformal RT. The PTV included enhancing tumour and post-operative cavity with a 2 cm margin. At a median follow-up of 20 months, the median OS was 15.6 months. No significant increase in toxicity was observed [35].

Morganti et al [36] reported on an Italian Phase 1 dose-escalation study of HFRT in 19 patients with GBM treated with concurrent and adjuvant TMZ. The median age was 59 years; 12 patients underwent GTR, 6 patients had STR and 1 patient had biopsy alone. 3 patients were in RPA Class III, 13 patients were in Class IV and 3 in Class V. The PTV1 included the GTV (enhancing tumour or surgical cavity) plus a 1.5 cm margin, and the PTV 2 included the area of GTV and surrounding oedema with a margin of 1.5 cm. The treatment was delivered in 25 fractions with the dose to PTV1 escalated in three dose levels (60 Gy, 62.5 Gy, 65 Gy) while maintaining the dose for PTV2 constant at 45 Gy. The study reported no DLT and the pattern of recurrence was predominantly central, with only two patients relapsing outside the PTV1 and one patient developing marginal recurrence. The median PFS was 12 months. The MS was 20 months with actuarial 1 year and 2 year OS of 81.9% and 28.9%, respectively [36].

## Discussion

Previous dose-exploratory studies established the dose schedule of 60 Gy delivered in 2.0 Gy per fraction as the standard of care in patients with GBM. Further dose escalation using standard fractionation and conformal techniques has shown no survival benefit [37, 38]. Furthermore, Phase 3 studies evaluating the role of $^{125}$I interstitial implant or stereotactic radiosurgical boost following conventional EBRT have failed to show survival advantage [39–41]. Similarly, investigation of alternative radiation schedules including hyperfractionation to a total dose of 72 Gy reported no specific benefit [42].

In this article we have reviewed the effects of HFRT based on the probable level of dose intensity achieved as defined by the tumour BED using the simplistic LQ model. It has been shown by Brenner [43] that the LQ formalism is an appropriate methodology for determining isoeffective doses at larger doses per fraction, which is reasonably validated up to 10 Gy per fraction and may also be reasonable to use up to 18 Gy per fraction. In contrast to earlier empirical methods of isoeffect calculation such as cumulative radiation effect [44], nominal standard dose [45] or time dose fractionation [46], the LQ model has become the preferred method owing to its use of biologically based parameters.

The LQ model incorporates the use of tumour doubling time (TDT) as a potential determinant of overall tumour BED. There are few reliable estimates of *in vitro* TDT for GBM and their applicability to clinical situation remains unclear. We analysed the effect of varying TDT on tumour BED using the LQ model and $\alpha$ and $\beta$ estimates mentioned previously (see Methods and materials) across a range of different doses per fraction (Figure 1). Using the above calculation, the biological effect of conventional RT is distinctly reduced in rapidly proliferating tumours (doubling time of <10 days) but subsequently the effect plateaus, with no obvious difference in tumour BED with further increase in TDT. By contrast, the BED from radiation schedules incorporating higher doses per fraction demonstrates less dependence on changes in TDT, which indicates the possibility of a therapeutic benefit for HFRT compared with conventional fractionation, particularly in rapidly proliferating tumours.

The initial development of HFRT in patients with GBM was purely driven by the perspective of reducing overall treatment time in the poor-prognosis subgroup of

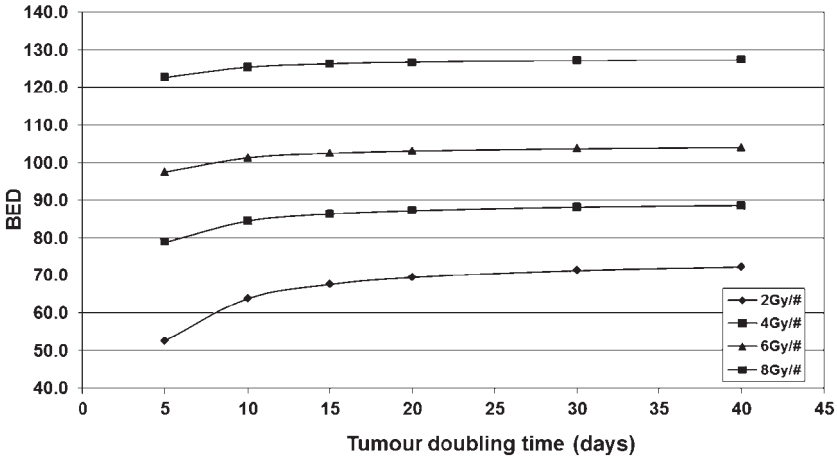


**Figure 1.** Effect of tumour doubling time on tumour biological effective dose (BED) with varying dose per fraction. The individual curves illustrate the tumour BED for prescribed dose of 60 Gy at different doses per fraction (2, 4, 6 and 8 Gy).

patients. These studies employed a suboptimal therapeutic radiation dose, but still showed efficacy comparable with conventional fractionation, which has been confirmed in three different randomised studies. The therapeutic potential of truncated HFRT schedules has always remained under close scrutiny, with the apparent efficacy in poor-risk patients often attributed to the natural history of the disease, which in the opinion of many was unlikely to be altered by the use of more aggressive treatment protocols. Hulshof et al [27], reporting on the results of a Dutch randomised series, strongly argued that the therapeutic efficacy of HFRT may indeed represent a true radiobiological effect. Floyd et al [28] argued that, unlike most other tumours that are thought to follow the early-responding tissue pattern, GBMs are relatively radioresistant and may respond more like late-responding neural tissue. Furthermore, pre-clinical studies in GBM cell lines have suggested that tumours harbouring mutations in the p53 tumour suppressor gene may behave like late-responding tissues with resistance to conventionally fractionated irradiation [47, 48]. TP53 mutations have been reported in more than 50% of GBM tumours and shown to be associated with higher degrees of invasiveness and aggressiveness [49, 50].

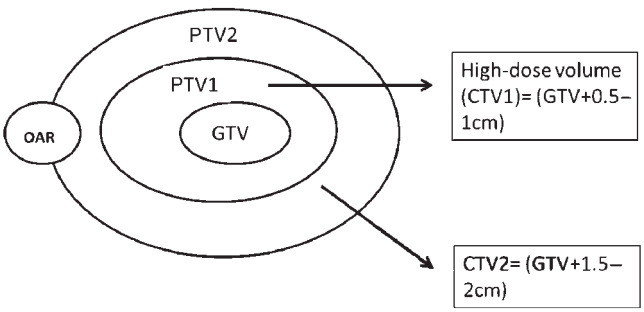


**Figure 2.** Principles of intensity-modulated radiotherapy (IMRT)-based planning for dose-escalated HFRT. The clinical target volumes include a high-dose region (PTV1) surrounding the gross tumour volume (GTV) with a 0.5–1-cm margin and PTV2 with a margin of 1.5–2 cm around the GTV. The two regions are prescribed differential doses using IMRT, with the high-dose area receiving higher tumour biological effective dose from increased dose and higher fraction size. This technique is inappropriate for tumours in close proximity to critical structures. PTV, planning target volume; OAR, organ at risk.

The last decade has witnessed the rapid evolution of IMRT, which is now considered the standard of care for several tumour sites. In brain tumours, IMRT has a particular advantage for improving the dose conformity and sparing critical neighbouring or adjoining normal tissues when compared with conventional RT. Previous IMRT clinical series have reported excellent compliance and low rates of toxicity [51]. Subsequently, few investigators have attempted a novel approach for dose escalation in GBM using IMRT-based hypofractionation.

Most studies of dose-escalated HFRT using IMRT have been single-arm Phase 1 prospective series, and have employed a varying range of dose schedules. However, these studies have followed the general principle of using multilayered PTV definition with dose escalation around the central area of enhancing tumour and surgical cavity (GTV+0.5–1 cm) and limited dose delivery to the surrounding brain parenchyma (Figure 2). The above pattern of volume definition represents a significant deviation from the most commonly employed RTOG protocols, which recommend a margin of 2.5–3.0 cm around the primary tumour and inclusion of the $T_2$ weighted abnormality (oedema) within the target volume. The practice for using larger target volumes is supported by previous studies showing viable tumour cells in the oedematous region following stereotactic biopsy [52–54]. However, the dominant pattern of post-RT failure remains central or immediately adjacent to the contrast-enhancing mass [55]. In the series from the University of Michigan, Ann Arbor, MI, of 23 patients treated with a dose of 90 Gy, most ($n$=18) relapsed within the 95% isodose line [38]. Similar results have been obtained from other dose-escalation studies [39–41]. Interestingly, despite achieving significant dose escalation around the primary tumour, most studies of dose-escalated HFRT still continue to show a central pattern of tumour recurrence emphasising the need for treating the tumour area (GTV) to maximum permissible dose.

Three different studies of high-dose HFRT have reported on the paradoxical phenomenon of improved survival in patients developing radiation necrosis at site of primary tumour [28, 30, 33]. The above phenomenon is not new and was highlighted by some of the earlier dose-escalation studies. The Northern California Oncology Group study evaluating the role of brachytherapy boost after conventional RT reported a paradoxical survival

benefit in patients developing radiation necrosis, and the authors speculated that focal necrosis may be an inevitable result of effective treatment of these tumours [56]. Similarly, Fitzek et al [57] showed an increase in MS from improved local control in patients developing central radionecrosis [57]. However, the above studies do not comment on the possible benefit from the second debulking surgery performed in these patients which may have confounded the results.

Most radical HFRT regimes are aimed at achieving a high tumour BED dose around the enhancing tumour, and therefore radiation necrosis is likely to be more frequently observed with these dose schedules. The toxicity criteria of RTOG and EORTC have defined clinically or radiographically suspected radionecrosis as Grade 4 toxicity. However, most patients diagnosed with radiation necrosis in the above studies underwent craniotomy for worsening radiological abnormality and remained asymptomatic. Furthermore, the probable association with improved survival would strongly argue against adopting a blind approach for classifying radiation necrosis as a Grade 4 toxicity. The Common Terminology Criteria for Adverse Events, v. 3, classifies radiation necrosis based on the level of symptoms and effect on overall function, which may be a more appropriate assessment tool in the above situation [58].

The main concern with the use of HFRT relates to the risk of inducing significant late toxicity from damage to critical organs, particularly the optic nerves, chiasm and brain stem. Most series of HFRT have reported no significant increase in the risk of acute or late toxicity. However, the study by Chen et al [33] reported visual loss in one patient at 7 months after RT. The review of RT plan revealed higher-than-recommended maximal dose to the left optic nerve (51.6 Gy, 3.4 Gy per fraction), right optic nerve (49.2 Gy, 3.3 Gy per fraction) and optic chiasm (45 Gy, 3 Gy per fraction). The possibility of long-term neural toxicity represents a significant but potentially avoidable risk of hypofractionated schedules. In view of the devastating consequences from damage to critical structures it is imperative that all HFRT protocols incorporate strict dose limits for organs at risk (OARs), which may automatically imply exclusion of tumours in close proximity to critical structures. However, the smaller margins used for defining the PTV1, combined with the use of highly conformal radiation technologies (IMRT), should facilitate the use of HFRT in most patients.

Most prospective studies of dose-escalated HFRT using IMRT were designed as safety and feasibility studies, but have reported on long-term survival as a secondary end point. However, the interpretation of outcome data is limited by their small sample size and significant heterogeneities in patient population and the employed dose schedules. Nevertheless, a careful review of the data reveals some interesting and consistent trends. There appears to be a clear dose–response relationship, with studies employing higher tumour BED of more than 90 $Gy_8$ showing favourable effect on local control and OS compared with historical controls. For example, the Phase 1 dose-escalation study reported by Iuchi et al [30] employed extreme levels of hypofractionation, with tumour BED ranging from 80 to 140 $Gy_8$, and showed improved local control, with only 6/25 (25%) patients developing local recurrence (LR) compared with approximately two-thirds in a parallel cohort of patients treated with conventional RT. Interestingly, the study reported CSF dissemination as the commonest mode of relapse. The study reported 1 and 2 year survival rates of 71.4% and 55.4%, respectively [30]. Similarly, the dose-escalation study reported by Monjazeb et al [31] employed three dose levels, with tumour BED ranging from 90 to 105 $Gy_8$, and reported a MS of 13.6 months, with 1 year and 2 year survival rates of 55% and 19%, respectively [31].

More interesting have been the results of combining HFRT with TMZ. The Japanese series reported by Terasaki et al [35] showed an MS of 15.6 months despite using a relatively modest dose of 45 Gy in 15 fractions. The series from McGill University reported an MS of 14.6 months for the entire study population [34]. However, the MS for those with RPA Class III–IV (comparable with patient population in the EORTC/NCIC study) was 17.9 months, compared with 12.9 months for those with Class V–VI. Two studies of dose-escalated HFRT combined with concurrent and adjuvant TMZ reported an MS of 20 months [33, 36].

The improved outcome from the above studies can possibly be explained by the emerging data on the underlying molecular mechanisms of TMZ-induced radiosensitivity. Chakravarti et al [59] reported on the results of a pre-clinical study combining TMZ with RT in a panel of GBM cell lines expressing differential levels of MGMT. TMZ enhanced radiation response in cell lines without detectable MGMT expression by the inhibition of DNA repair pathways and increasing the level of radiation-induced damage and unrepaired DNA double-strand breaks. The observed effect was dose-dependent, and more robust with increasing fraction size. The above effect was not observed in MGMT expressing cell lines, which is consistent with the results from the McGill series that reported on the prognostic significance of MGMT methylation status for determining the response after HFRT. Furthermore, the radiosensitising effect was limited to tumour cell lines with no effect on normal human astrocytes.

In summary, several studies have evaluated the role of HFRT in patients with newly diagnosed GBM. However, the majority of these studies are predominantly retrospective or relatively small single-arm prospective series that add little to the overall quality of evidence. In addition, interpretation of data is confounded by significant heterogeneity in patient characteristics and range of dose schedules employed. There have been no properly designed studies with adequate power to demonstrate survival advantage of HFRT compared with conventional RT. Notwithstanding the above limitations, HFRT appears to be a safe and feasible strategy for patients with GBM. Most studies have reported no significant increase in acute or late toxicity with the use of modern high-precision radiation technology, provided adequate precautions are followed for the adequate shielding of OARs beyond tolerance. More recently, data has emerged from Phase 1 studies combining HFRT with concurrent and adjuvant TMZ, and a trend has been reported towards improved survival outcomes compared to historical controls. In a disease with dismal prognosis, the use of HFRT is a particularly attractive option from the patient's perspective

for reducing the overall treatment time, the importance of which should not be underestimated.

## Conclusion

HFRT was initially developed as a pragmatic concept in poor-risk patients, but more recent studies have explored HFRT as a novel approach for achieving intratumoral dose escalation. Based on the predominant central pattern of tumour recurrence, the above studies have focused on escalating the dose around the central enhancing tumour and employed relatively small margins for defining the high-dose volume. The data emerging from the above studies is encouraging and strongly argues for further research and randomised study of IMRT-driven dose-escalated HFRT and TMZ compared with conventional CRT. The proposed study should include the treatment-related outcomes (LR, PFS, OS) as the key primary end points, with the effect on quality of life and overall toxicity as important secondary end points. In addition, in view of the complexity of the RT techniques involved it will be extremely important to have strict radiotherapy quality assurance incorporated into the trial protocol.

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