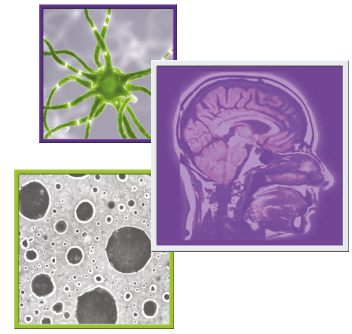
Research Article

For reprint orders, please contact: reprints@futuremedicine.com

CNS Oncology



Can 3D-CRT meet the desired dose distribution to target and OARs in glioblastoma? A tertiary cancer center experience

Narendra Kumar[1], Srinivasa GY*[,1], Chinna B Dracham[1], Treshita Dey[1], Renu Madan[1], Divya Khosla[1], Arun Oinum[1] & Rakesh Kapoor[1]

[1]Department of Radiotherapy & Oncology, Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India

*Author for correspondence: Tel.: +91 980 580 3262; drsrinivasagowda@gmail.com

Aim: The purpose of the study is to perform a dosimetric analysis of the doses received by planning target volume and organ at risks in the postoperative glioblastoma by using 3D-conformal radiotherapy to a total dose of 60 Gy in 30 fractions. **Materials & Methods:** All patients received concurrent temozolomide every day, and this was followed by adjuvant temozolomide of 5 days of treatment per month. **Results:** More than 98% of patients were treated with a dose of 60 Gy. Doses were analyzed for the normal whole brain, tumor volume, as well as all the organs at risk. **Conclusion:** Given the grave prognosis and the limited survival of glioblastoma despite the best treatment available, makes 3D-conformal radiotherapy an equally acceptable treatment option.

First draft submitted: 24 April 2020; Accepted for publication: 3 June 2020; Published online: 18 September 2020

Keywords: 3D-conformal radiotherapy (3D-CRT) • adjuvant TMZ • cochlea • concurrent temozolomide (TMZ) • conformity index • dose spillage • dosimetric analysis • homogeneity index • optic chiasm • postoperative glioblastoma (GBM)

Glioblastoma (GBM) is the most aggressive type of brain tumor, accounting for 75% of all high-grade gliomas. The incidence of GBM is increasing by approximately 1% per year, likely due to the aging of the population [1]. The treatment consists of maximal surgical resection followed by concurrent temozolomide (TMZ) daily along with external beam radiation of 60 Gy in 30 fractions over a period of 6 weeks followed by adjuvant TMZ for 5 days of treatment per month. Prognosis remains poor despite surgery followed by concurrent chemoradiation and adjuvant treatment with a median overall survival of 14.6 months and 3-year overall survival of 16.4% [2]. Local recurrence is the most common pattern of failure after treatment, and a common cause for recurrence is the inability to deliver an adequate dose of radiation to the target volume [3,4]. The proximity of normal critical structures to the target volume, such as the optic chiasm, optic nerve and brain stem, is the main reason that limits delivery of an adequate dose of radiation to the tumor tissue. Conventional radiation was the norm until the development of computed tomography (CT), but the potential to cause toxicities induced by radiation to the organs at risk (OAR) limited delivery of adequate doses. With advancement of 3D conformal radiotherapy (3D-CRT), the ability to deliver dose to the target tissue has been increased with limiting dose to the normal critical structures [3]. Intensity-modulated radiotherapy (IMRT) provides similar results in terms of target volume coverage when compared with 3D-CRT, and it did not show any improvement in the local tumor control or overall survival when compared with 3D-CRT [1,5]. The purpose of the present study was to do a dosimetric analysis of the doses received by planning target volume (PTV) and OARs in the postoperative setting by using 3D-CRT to a total dose of 60 Gy in 30 fractions over 6 weeks.

Methods

This is a retrospective study of postoperative cases of GBM treated with surgery followed by concurrent chemoradiation and adjuvant TMZ at our institute from January 2011 to December 2016. Out of 163 patients, 150 patients

Future Medicine

Table 1. Organs at risk and their tolerance dose including primary and secondary criteria.

Organs at risk	Constraints	Secondary criteria
Optic chiasma	Dmax <54 Gy	Dmax <60 Gy
Optic nerve	Dmax <54 Gy	Dmax <55 Gy
Brainstem	Dmax <54 Gy	Dmax <60 Gy, $V_{59\ Gy}$ <10 cc
Eyeball	Dmax <45 Gy Dmean <18 Gy	
Lens	Dmax <6 Gy	Dmax <10 Gy
Cochlea	Dmean ≤45 Gy	Dmean <50 Gy
Temporal lobe	Dmax ≤60 Gy	$V_{65\ Gy}$ <1 cc

Dmax: Maximum dose received by a particular point; Dmean: Mean dose received by the organ; V_{59}: Volume receiving 59 Gy; V_{65}: Volume receiving 65 Gy.

who underwent surgery in the form of gross-total excision, near-total excision, subtotal excision or biopsy, depending on the disease extension and location of the tumor, followed by adjuvant 3D-CRT along with concurrent TMZ were included in the analysis and the rest who received palliative treatment were excluded. All patients received concurrent TMZ (75 mg/m^2) daily 1 h before radiation for 7 days per week from the first day to the last day of radiotherapy, and this was followed by adjuvant TMZ (175 mg/m^2) 5 days per month [2].

Radiotherapy planning

Planning CT scans were taken with patients in supine position and immobilized with a three clamp orfit cast. Imaging acquisition protocol required a slice thickness of 2.5 mm in a multislice CT scanner (GE Healthcare Technologies, WI, USA), both immediately (within 15 s) and delayed, in other words, 10 min after injection of contrast [6]. The images were then transferred to the Eclipse™ treatment planning system (v.8.6, Varian Medical Systems, CA, USA). Planning CT images were fused with postoperative magnetic resonance (MR) images that were taken a few days before starting the radiation. Contouring was done as per MD Anderson Cancer Centre (TX, USA) guidelines, and there are studies published from our institute [7,8]. We followed our institutional protocol in delineating target volumes and OAR. The gross tumor volume (GTV) included postoperative cavity and gross residual tumor seen on the CT images and fused MR images. The clinical target volume (CTV) includes 2.0 cm isotropic margin all around the GTV along with edema surrounding the tumor following anatomical boundaries. PTV was generated by giving a 0.5 cm symmetrical margin around the CTV. CTV boost was created by giving a 0.5 cm margin around the GTV and PTV boost was generated by giving a 0.5 cm margin around CTV boost.

OARs, including the optic chiasm, right and left optic nerves, right and left temporal lobes, brain stem, right and left eye, right and left lens and right and left cochlea, were contoured. 3D-CRT plans were generated by using appropriate non-coplanar beams, one vertex and two lateral fields (total of three fields) with appropriate wedges in most of the cases with 6 MV photons (x-ray) using linear accelerators. In all cases with non-coplanar beams, a vertex field was used. Only coplanar beams were used mainly for planning tumors of the posterior fossa. An initial dose of 46 Gy in 23 fractions were prescribed to the PTV, followed by 14 Gy in seven fractions to the PTV boost (total dose of 60 Gy in 30 fractions over 6 weeks) as per the institution protocol. Plans were optimized to deliver prescribed dose to more than 95% of PTV and maximum dose in the target volume not to exceed 107% of prescribed dose international commision on radiation units and measurements (ICRU) : 50 and 62. Dose volume histograms were generated for qualitative and quantitative assessment of generated plans and evaluated for all the OARs before delivering treatment. Evaluation of dosimetric data was done, in other words, doses received by target volumes and OARs using Quantitative Analysis of Normal Tissue Effects in Clinics (QUANTEC) parameters listed in Table 1 [9,10,11]. If the dose constraints of OARs were not met, depending on the location and burden of the tumor, we prioritized the OARs surrounding the tumor and plans were optimized accordingly, for example, for tumors close to or invading the left optic nerve, instead of under dosage, we have preferred treating till 60 Gy after prioritizing the right optic nerve to preserve vision. All 3D-CRT plans were analyzed in terms of PTV coverage, conformity index (CI), homogeneity index (HI) and OAR dose volume parameters, as per ICRU 83. Several definitions of CI are available, but we used the Radiation Therapy Oncology Group (RTOG; PA, USA) definitions to calculate the CI [12,13].

CI (RTOG) = Reference isodose volume/target volume

HI (RTOG) = Maximum isodose in the target/reference isodose

Quality of coverage (RTOG) = Minimum isodose around the target/reference isodose.
In this study, 95% isodose curve was considered as the reference isodose.

Statistics

Statistical analysis was done with the Statistical Program for Social Sciences (SPSS v 23, IBM Corp., NY, USA). Descriptive analysis was done for dosimetric data and demographic data. Summary of statistics including mean, median, range and standard deviation (SD) were obtained.

Results

A retrospective analysis was done on 150 patients of GBM radically treated in the Department of Radiotherapy and Oncology at the Postgraduate Institute of Medical Education & Research, Chandigarh (India) between 2011 and 2016 with external beam radiotherapy and TMZ (concurrent ± adjuvant) after maximal safe surgical resection. The median age of study population at diagnosis was 50 years (range: 18–74 years). Most commonly, patients presented with features suggestive of raised intracranial pressure (57.9%), followed by seizures (20%). Median duration of symptoms was 8 months (range: 1–5 months).

The most common location of a tumor was in the frontal lobe (41%), followed by the temporal lobe (18.6%) and rarely the cerebellum and corpus callosum. Only one patient underwent surgery for decompression, whereas 51 and 42% of patients underwent near-total excision and gross-total excision, respectively. The whole-brain volume of these patients was analyzed (median: 1306.35 cc, range: 143–1306 cc). All patients were planned by external beam radiation using six MV photons. None of them were planned with IMRT. More than 98% of patients were treated with a dose of 60 Gy (46 + 14 Gy boost), the rest received only 54 Gy in view of their proximity to critical organs, for example, brainstem and spinal cord. Overall, 61% of patients received TMZ concurrently with radiation, while rest were treated with radiotherapy alone, the main reason being nonaffordability. The majority of patients completed radiation without any interruptions, except for 6.4% cases where a break was noted citing personal issues and worsening neurological symptoms. Following completion of radiotherapy, about 57% of patients received adjuvant TMZ for the first 5 days every 4 weeks. This low proportion was due to poor patient compliance, poor general condition and early disease progression. Only 13% of patients completed 6–12 cycles, with 13.6% continuing beyond 12 cycles. Around 31% of patients received less than six cycles of TMZ post-radiotherapy (Table 2).

Doses were analyzed for the normal whole brain, tumor volume and all the OARs. Dmax and Dmean were noted for all. For PTV, dose received by 98 and 2% volumes were also noted (D98 and D2). Mean, median and SD were calculated. The mean CI and HI were also calculated.

Dosimetric data of tumor

The mean GTV volume of the tumors measured on planning CT-MR fusion imaging (T1 gadolinium) was 85.05 cc (range: 9.6–291 cc). PTV volume was calculated on the same imaging (mean: 467.92 cc, range: 62.6–982 cc). The mean dose received by GTV was 60.553 Gy (SD: 0.5859 Gy), PTV was 58.534 Gy (SD: 1.4515 Gy). For PTV, mean D98 was 56.406 Gy (SD: 4.45 Gy), and D2 was 61.707 Gy (SD: 3.695 Gy). The mean dose received by whole brain was 37.114 Gy (SD: 8.259 Gy), and the maximum dose (Dmax = maximum point dose) was 62.404 Gy (SD: 3.335 Gy) (Table 3).

Dosimetric data of OARs

In our study, the average Dmax of the brainstem was 53.165 Gy (SD: 11.33 Gy, median: 57.8 Gy). The mean doses to the right and left eyes were 7.805 and 7.809 Gy, respectively, and the maximum doses were 25.597 and 25.516 Gy, respectively. The maximum dose obtained by the right and left optic nerves were 38.114 and 36.988 Gy, respectively, and 37.987 Gy for optic chiasma. The Dmax (maximum point dose) for lens were 4.881 Gy (right) and 5.019 Gy (left). The temporal lobes received a maximum dose of 55.66 Gy (right) and 55.816 Gy (left). The mean doses received by right and left cochlea were 33.201 and 32.332 Gy, respectively (Table 4).

Treatment planning parameters

The mean CI was 1.10 with a SD of 0.11 (median: 1.07) that was well within our defined limits. The mean HI was 0.101 with SD of 0.078 (median: 1.19). The average beam-on time for each patient was 1.324 min (SD: 0.289 min). The mean quality of coverage index was 0.92598 with a SD of 0.586 and a median of 0.944. The

Table 2. Patient and treatment characteristics including the type of surgeries and the details of adjuvant treatment received.

Characteristics		Frequency
Sex	Male	94 (67.1%)
	Female	46 (32.9%)
Age	<60 years	116 (82.9%)
	>60 years	24 (17.1%)
Symptoms	Raised ICT	81 (57.9%)
	Seizures	28 (20%)
	Sensory/motor deficits	21 (15%)
	HMF deficit	10 (7.1%)
Site	Frontal	57 (40.7%)
	Parietal	13 (9.3%)
	Temporal	26 (18.6%)
	Occipital	2 (1.4%)
	Cerebellum	1 (0.7%)
	Corpus callosum	1 (0.7%)
	Others	40 (28.5%)
Surgery	GTE	59 (42.1%)
	NTE	71 (50.7%)
	STE	9 (6.4%)
	Decompression	1 (0.7%)
EBRT dose	60 Gy	138 (98.6%)
	54 Gy	2 (1.4%)
TMZ status	Yes (concurrent/adjuvant)	100 (71.4%)
	No	40 (28.6%)
Concurrent TMZ	Yes	86 (61.4%)
	No	54 (38.6%)
Adjuvant TMZ cycles	Yes	60 (42.9%)
	<6	43 (30.7%)
	6–12	18 (12.9%)
	>12	19 (13.6%)
Treatment breaks	Yes	9 (6.4%)
	No	130 (92.9%)

EBRT: External beam radiation; GTE: Gross total excision; HMF: Higher mental function; ICT: Intracranial tension; NTE: Near total excision; STE: Subtotal excision; TMZ: Temozolomide.

Table 3. Tumor characteristics and the dose received by the target volumes (all patients including two who received a total of 54 Gy are included in the analysis).

Characteristics	Mean	SD	Median
GTV volume	85.049	59.402	71.5
PTV volume	467.918	194.3745	446.575
Whole brain volume	1289.191	143.194	1306.35
GTV Dmean	60.553	0.5859	60.6
PTV Dmean	58.534	1.4515	58.65
PTV D98	56.406	4.45	58.4
PTV D2	61.707	3.695	62.2
Whole brain Dmax	62.404	3.335	62.9
Whole brain Dmean	37.114	8.259	36.65

D2: Dose received by the 2% target volume; D98: Dose received by the 98% of target volume; Dmax: Maximum dose received by a particular point; Dmean: Mean dose received by the organ; GTV: Gross tumor volume; PTV: Planning target volume; SD: Standard deviation.

Table 4. Mean dose and maximum dose received by normal structures surrounding the target volumes.

Organ	Mean (Gy)	SD	Median (Gy)
Brainstem Dmax	53.165	11.3302	57.8
RT eye Dmax	25.597	19.868	25.4
RT eye Dmean	7.805	7.9044	5.35
LT eye Dmax	25.516	19.5253	25.35
LT eye Dmean	7.809	7.6432	5.15
RT optic nerve Dmax	38.114	21.426	44.75
LT optic nerve Dmax	36.988	21.0452	42.15
Optic chiasma Dmax	37.987	19.645	40.15
RT lens Dmax	4.881	6.9729	3.1
LT lens Dmax	5.019	6.9215	3.05
RT cochlea Dmean	33.2012	20.64653	39.174
LT cochlea Dmean	32.332	21.173	37.884
RT temporal Dmax	55.66	8.7378	58.9
LT temporal Dmax	55.816	7.8919	59.1

Dmax: Maximum point dose; Dmean: Mean dose received by the organ; LT: Left; RT: Right; SD: Standard deviation.

Table 5. Table showing different planning indexes and other parameters for the 3D-conformal radiotherapy, plans and their values.

Parameters	Mean	SD	Median
Conformity index	1.1008	0.10974	1.0691
Homogeneity index	0.101	0.078	0.069
Beam on time (minutes)	1.324	0.289	1.19
Quality of coverage	0.92598	0.0586	0.944622
Spill factor	2.6668	0.8392	2.2491

SD: Standard deviation.

mean spillage factor was 2.6668 with a SD of 0.8392 and a median of 2.2491. Quality assurance procedures were done using Winston Lutz test tool, and this was subsequently verified by Isocal phantom (Table 5).

Discussion

GBM can develop in various locations in the brain; some tumors may present far from a critical structure, while others can be located in the vicinity of many highly radiosensitive OARs (e.g., optical pathways, brainstem), ultimately resulting in a complex treatment scenario that makes radiotherapy planning challenging. Quality assurance regarding the randomized Phase III EORTC 26981/22981 and NCIC CE3 trial clearly showed that adequate coverage of target tissue along with sparing of OARs poses a real challenge in GBM treatment by radiotherapy [14]. IMRT planning results in high conformal dose distribution and significantly reduced dose to the remaining healthy brain tissue. Keeping in mind, the grave prognosis associated with these high-grade gliomas and their high propensity of recurrence, late toxicities related to radiation rarely is a problem. The median survival of such patients with the standard therapy of radiation and TMZ (concurrent + adjuvant) is 14.6 months, and almost all patients develop recurrence within 2 cm of primary tumor, so symptoms arising due to late toxicities are not commonly seen [4,15]. In this study, all patients were planned by 3D-CRT ensuring adequate tumor coverage, which is the primary aim of treatment, and a dosimetric analysis was done for evaluation (Table 5). The dose prescribed was 46 Gy in 23 fractions in the first phase, followed by a boost of 14 Gy in seven fractions as per the institution protocol.

In an ideal scenario, the CI should be equal to 1 and HI should be ≤ 2. CI <1 indicates that target volume is not adequately irradiated, and >1 indicates that irradiated volume is greater than the target volume and irradiates part of healthy tissue. RTOG guidelines define CI values between 1 and 2 since the value of 1 can be rarely achieved. HI ≤ 2 is considered ideal, between 2 and 2.5 is consider as minor and >2.5 as a major treatment protocol violation. There are two major drawbacks for using indices for plan evaluation. First, the reference isodose curve is not standardized. Second, the ratio of a relatively regular isodose volume and an irregular tumor contour maybe 1 that

Table 6. Comparison of doses received by normal structures in different studies using 3D conformal radiotherapy, intensity-modulated radiotherapy and volumetric-modulated arc therapy plans.

Organ	Chan *et al.* [3]		Thibouw *et al.* [1]		Ibis *et al.* [9]			Our study
	3D-CRT	*IMRT*	*3D-CRT*	*IMRT*	*3D-CRT*	*IMRT*	*VMAT*	*3D-CRT*
Brainstem Dmax	59	58	53.2	54.8	54.6	50	47.2	53.165
Optic chiasma Dmax	49	43	40.4	52.9	44	41.7	41.7	37.987
Optic nerve Dmax	24	23	17.25	34.2	44.2	31	C/L: 23.9 I/L: 37.3	43.45
Lens Dmax	3.1	2.9	–	–	4.9	6	C/L: 6.2 I/L: 6.8	3.07
Whole brain Dmean	32	27	27.8	25.7	32.3	21.6	23.8	37.114
Conformity index	–	–	1.53	1.25	2.3	1.1	1	1.1
PTV D98	–	–	55.5	57.5	–	–	–	56.406
PTV D2	–	–	62.4	61.6	–	–	–	61.707

3D-CRT: 3D conformal radiotherapy; C/L: Contralateral; Dmax: Maximum point dose; Dmean: Mean dose received by the organ; D2: Dose received by 2% of volume; D98: Dose received by 98% of volume; I/L: Ipsilateral; IMRT: Intensity modulated radiotherapy; PTV: Planning target volume; VMAT: Volumetric modulated arc therapy.

does not give the actual scenario of tumor coverage [13]. In our study, the mean CI obtained was 1.1 (SD: 0.109), and the mean HI was 0.101 (SD: 0.078). For the quality of coverage index, at least 90% isodose should cover the target volume. If it is covered by 80%, then it should be considered as minor violation otherwise a major protocol violation [13].

Analysis by Lorentini *et al.* on 17 GBM patients treated with both 3D-CRT and IMRT showed that IMRT led to better tumor coverage with almost similar dosage to OARs and a significantly low healthy brain irradiation [16]. In this study, patients were subdivided based on whether there was any overlap between PTV and dose-limiting normal tissues. It was seen that there was no statistically significant difference in the doses received by PTV, brainstem or optic apparatus when there was no overlap between two volumes and 3D-CRT in such patients was equally well planned as IMRT. However, differences were noticed between the two plans in case of overlapping volumes where IMRT resulted in significantly low doses to the brainstem and ipsilateral optic apparatus. In a retrospective study by Thibouw *et al.*, 220 patients with GBM treated with 3D-CRT and IMRT [1]. Dosimetric and clinical parameters with survival data were compared between the two. They concluded better dose conformity in those treated by IMRT, although Dmax of the brainstem, optic apparatus and cochlea were higher. The CI in those treated by IMRT in Thibouw *et al.* was 1.25, which was comparable to our patients treated by 3D-CRT, having a CI of 1.1. In the toxicity analysis, grade 1 and 2 toxicities were significantly higher in the 3D-CRT arm, grade 3 or higher toxicities were more in IMRT, but the frequency was very low and hence not considered significant. However, the CI value is the same as that achieved by IMRT in the analysis by Ibis *et al.* They concluded lower midline OAR dosage with IMRT and volumetric-modulated arc therapy (VMAT) compared with 3D-CRT. The CI was 2.3 for 3D-CRT, 1.1 for IMRT and 1 for VMAT, which was also achieved in our study by 3D-CRT plans [17]. The study by Chan *et al.* at Memorial Sloan Kettering Cancer Center (NY, USA) on five patients planned by 3D-CRT and IMRT with a dose of 59.4 Gy at 1.8 Gy per fraction concluded IMRT (including simultaneous integrated boost) to be better than 3D-CRT. However, here 3D-CRT plans resulted in same dose homogeneity as with IMRT [18].

Another dosimetric study by MacDonald *et al.* concluded better target dose homogeneity and less dose to the OAR with IMRT, thus improving the therapeutic ratio. However, the researchers did not comment on the proximity of the tumor to the critical organs in this patient group [19]. A study by Wagner *et al.* has summarized the optimal use of VMAT, IMRT and 3D-CRT with respect to the tumor location [20]. If the PTV is not close to the OARs, then 3D-CRT gives adequate target dose distribution. If PTV and OARs are close, then using IMRT or RapidArc™ (Varian Medical Systems) was advised to attain better homogeneity. Between IMRT and RapidArc, RapidArc had a very short treatment time but resulted in higher low-dose areas. 3D-CRT was also recommended for the younger population due to significantly decreased low-dose volumes.

The dose constraints that were used for plan evaluation were same as that of QUANTEC data. 3D-CRT plans conformed to the dose constraints in the majority of patients. Only 1.4% of patients required a dose modification owing to high doses arising from overlap or proximity to OARs, and maybe these patients might have benefitted from IMRT. A comparison is given below between the mean doses within tumor and OARs in the available literature with that of our study in Table 6. The doses achieved at our institute with 3D-CRT plans were almost at

par with those achieved by 3D-CRT, and slightly more than IMRT plans in the previous studies. However, dose received by whole brain in our patients was much more than that of available literature.

It is important to the note that in most of the available literature mentioned here, IMRT plans were made only for dosimetric analysis and patients were treated with 3D conformal plans. Correlating this dosimetric analysis with survival data has shown conflicting results. A retrospective analysis by Burela *et al.* done on 80 patients of high-grade gliomas treated with 60 Gy by 3D-CRT, IMRT and RapidArc showed a survival benefit with lesser dose to normal brain that can be achieved by highly precise radiation techniques ($p = 0.022$) [21]. As is evident from Table 6, patients treated by 3D-CRT plans received a higher mean dose to normal brain, which also holds true for our study with a Dmean of 37.11 Gy. A retrospective dosimetric analysis by Hermanto *et al.* showed high-grade gliomas planned with IMRT resulted in better conformity without any increment in integral dose to brain or volumes of healthy brain tissue, which is exposed to lesser radiation doses [22]. Another study was done retrospectively by Huilgol *et al.* on 46 patients treated with 60 Gy of 3D-CRT and IMRT showed no difference in overall survival ($p = 0.66$) [23]. Thus, treating with intensity-modulated therapies have failed to show any significant improvement in either local control or overall and progression-free survival. Thus, the radiobiological effect is similar to both 3D-CRT and IMRT. The target coverage and OAR dose constraints were achieved with 3DC-RT plans in our study. However, IMRT has the potential to reduce mean whole-brain dose, but the beam on times are longer with IMRT, and additional safety checks and quality assurance are required before the start of treatment. Using VMAT, we can achieve a better dose homogeneity and conformity and also less beam-on time. However, in a tertiary care center like ours, where the patient load is high, use of 3D-CRT is justified as it is less time consuming and more convenient with similar local control. Multiple overlaps between OAR and PTV can be a criterion in which IMRT may be chosen over 3D-CRT.

The limitation of the present study is its retrospective nature. The study will have a bias in selecting the patients for the analysis. Due to its retrospective nature, we could not analyze the toxicities accordingly.

Conclusion

In the current study, we found that adjuvant 3D-CRT in cases of GBM is acceptable in terms of both target volume coverage and homogeneity. A total of 60 Gy can be safely prescribed by 3D-CRT, with IMRT to be reserved only for tumors with considerable OAR overlap. Considering the burden of disease and the limited survival of grade IV gliomas despite multimodality treatment, 3D-CRT is an acceptable treatment option for the majority.

Future perspective

With the introduction of image-guided radiotherapy, tomotherapy and PET-based planning, each of which are being used in the field of radiotherapy, the dose to the tumor can be increased with sparing of the critical structure. This may lead to an improvement in overall survival. Now, a day with the emergence of proton therapy, dose escalation to tumors residing in difficult positions can be achieved. Only with time, we will witness the actual benefit of proton therapy. Various molecular markers are being investigated, which might help us delineate the metabolically active tumor volume. An emphasis on translational research will help us in trying novel methods, which are as yet untested.

Author contributions

N Kumar provided substantial contributions to the conception or design of the work and final approval of the version to be published. GY Srinivasa also provided substantial contributions to the conception or design of the work, the acquisition, analysis or interpretation of data for the work and drafting the work or revising it critically for important intellectual content. CB Dracham contributed to the drafting the work or revising it critically for important intellectual content. T Dey drafted the work or revised it critically for important intellectual content. R Madan provided final approval of the version to be published. D Khosla was responsible for the agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. A Oinum revised the work critically for important intellectual content. R Kapoor was responsible for the agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations.

Summary points

- This is a retrospective study of postoperative cases of glioblastoma treated with surgery followed by concurrent chemoradiation and adjuvant temozolomide (TMZ).
- All patients received concurrent TMZ (75 mg/m^2) everyday 1 h before radiation for 7 days per week from the first to last day of radiotherapy. This was followed by adjuvant TMZ (175 mg/m^2) for 5 days of treatment per month.
- All 3D conformal radiotherapy (3D-CRT) plans were analyzed in terms of planning target volume coverage, conformity index and organs at risk dose volume parameters.
- More than 98% of patients were treated with a dose of 60 Gy (46 + 14 Gy boost), the rest received only 54 Gy in view of their tumor's proximity to critical organs.
- Following completion of radiotherapy, about 57% patients received adjuvant TMZ every 4 weeks. Only 13% patients completed 6–12 cycles, 13.6% continuing beyond 12 cycles. Around 31% patients received less than six cycles of TMZ post-radiotherapy.
- In the current study, we found that adjuvant 3D-CRT in cases of glioblastoma is acceptable in terms of target volume coverage and homogeneity.
- Intensity-modulated radiotherapy provides a better conformal dose distribution to the target tissue along with significant sparing of the dose-limiting critical organs in vicinity; however, given the grave prognosis and the limited survival of grade IV gliomas despite the best treatment available, 3D-CRT is an equally acceptable treatment option. In a country like India where we have increased patient load, we can spend less time on machine using 3D-CRT.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Thibouw D, Truc G, Bertaut A, Chevalier C, Aubignac L, Mirjolet C. Clinical and dosimetric study of radiotherapy for glioblastoma: three-dimensional conformal radiotherapy versus intensity-modulated radiotherapy. *J. Neurooncol.* 137(2), 429–438 (2018).

•• **In this retrospective study, they compared intensity-modulated radiotherapy (IMRT) and 3D-conformal radiotherapy (3D-CRT) plans in glioblastoma (GBM) patients, and importantly they did the survival analysis.**

2. Stupp R, Hegi ME, Mason WP *et al.* Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised Phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol.* 10(5), 459–466 (2009).

3. Chan JL, Lee SW, Fraass BA *et al.* Survival and failure patterns of high-grade gliomas after three-dimensional conformal radiotherapy. *J. Clin. Oncol.* 20(6), 1635–1642 (2002).

4. Hess CF, Schaaf JC, Kortmann RD, Schabet M, Bamberg M. Malignant glioma: patterns of failure following individually tailored limited volume irradiation. *Radiother. Oncol.* 30(2), 146–149 (1994).

5. Chen YD, Feng J, Fang T, Yang M, Qiu XG, Jiang T. Effect of intensity-modulated radiotherapy versus three-dimensional conformal radiotherapy on clinical outcomes in patients with glioblastoma multiforme. *Chin. Med. J. (Engl.)* 126(12), 2320–2324 (2013).

6. Kumar N, Vyas S, Salunke P *et al.* Hurdles in radiation planning for glioblastoma: can delayed-contrast enhanced computed tomography be a potential solution? *Asia Pac. J. Clin. Oncol.* 15(5), e103–e108 (2019).

• **It shows the importance of delayed CT scans in target delineation and can be an alternative to MRI in target delineation.**

7. Chang EL, Akyurek S, Avalos T *et al.* Evaluation of peritumoural edema in the delineation of radiotherapy clinical target volumes for glioblastoma. *Int. J. Radiat. Oncol. Biol. Phys.* 68(1), 144–150 (2007).

8. Kumar N, Kumar R, Sharma S *et al.* Impact of volume of irradiation on survival and quality of life in glioblastoma: a prospective, Phase II, randomised comparison of RTOG and MDACC protocols. *Neuro Oncol. Prac.* 7(1), 86–93 (2020).
9. Mayo C, Yorke E, Merchant T. Radiation associated brainstem injury. *Int. J. Radiat. Oncol. Biol. Phys.* 76(3), S36–S41 (2010).
10. Mayo C, Martel M, Marks L, Flickinger J, Nam J, Kirkpatrick J. Radiation dose-volume effects of optic nerves and chiasm. *Int. J. Radiat. Oncol. Biol. Phys.* 76(3), S28–S35 (2010).

• **It is a landmark study that showed does-volume effects of normal structures and their tolerance doses.**

11. Lawrence Y, Li X, el Naqa I *et al.* Radiation dose-volume effects in the brain. *Int. J. Radiat. Oncol. Biol. Phys.* 76(3), S20–S27 (2010).

• **It showed does-volume effects of normal structures and their tolerance doses, which are now used for evaluation of conformal plans.**

12. Shaw E, Kline R, Gillin M *et al.* Radiation Therapy Oncology Group: radiosurgery quality assurance guidelines. *Int. J. Radiat. Oncol. Biol. Phys.* 27(5), 1231–1239 (1993).
13. Feuvret L, Noël G, Mazeron JJ, Bey P. Conformity index: a review. *Int. J. Radiat. Oncol. Biol. Phys.* 64(2), 333–342 (2006).

•• **It showed the importance of conformity index and homogeneity index in the analysis of treatment plans.**

14. Ataman F, Poortmans P, Stupp R, Fisher B, Mirimanoff R-O. Quality assurance of the EORTC 26981/22981; NCIC CE3 intergroup trial on radiotherapy with or without temozolomide for newly diagnosed glioblastoma multiforme: the individual case review. *Eur. J. Cancer* 40(11), 1724–1730 (2004).
15. Stupp R, Mason W, van den Bent M *et al.* Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N. Engl. J. Med.* 352(10), 987–996 (2005).
16. Lorentini S, Amelio D, Giri M *et al.* IMRT or 3D-CRT in glioblastoma? A dosimetric criterion for patient selection. *Technol. Cancer Res. Treat.* 12(5), 411–420 (2013).
17. İbiş K, Akbaş U, Köksal C, Altun M. Comparison of three-dimensional conformal radiation therapy, intensity-modulated radiation therapy, and volumetric-modulated arc therapy in glioblastoma multiforme radiation therapy with EORTC target delineation. *Turk. J. Oncol.* 33(2), 65–72 (2018).

• **It showed the importance of volumetric-modulated arc therapy in achieving better conformity compared to IMRT and 3D-CRT along with sparing normal structures.**

18. Chan M, Schupak K, Burman C, Chui C, Ling C. Comparison of intensity-modulated radiotherapy with three-dimensional conformal radiation therapy planning for glioblastoma multiforme. *Med. Dosim.* 28(4), 261–265 (2003).

• **In the study, it showed 3D-CRT achieved same dose homogeneity as that of IMRT plans.**

19. MacDonald S, Ahmad S, Kachris S *et al.* Intensity modulated radiation therapy versus three-dimensional conformal radiation therapy for the treatment of high grade glioma: a dosimetric comparison. *J. Appl. Clin. Med. Phys.* 8(2), 47–60 (2007).
20. Wagner D, Christiansen H, Wolff H, Vorwerk H. Radiotherapy of malignant gliomas: comparison of volumetric single arc technique (RapidArc), dynamic intensity-modulated technique and 3D conformal technique. *Radiother. Oncol.* 93(3), 593–596 (2009).

• **The authors summarized the optimal use of volumetric-modulated arc therapy, IMRT and 3D-CRT with respect to the tumor location in this study.**

21. Burela N, Patni N. Outcome of high grade gliomas–an institutional experience. *Acta Med. Int.* 4(1), 66–73 (2017).
22. Hermanto U, Frija E, Lii M, Chang E, Mahajan A, Woo S. Intensity-modulated radiotherapy (IMRT) and conventional three-dimensional conformal radiotherapy for high-grade gliomas: does IMRT increase the integral dose to normal brain? *Int. J. Radiat. Oncol. Biol. Phys.* 67(4), 1135–1144 (2007).
23. Huilgol N, Haneefa A, Dusane R, Saluja V, Sridhar C. Retrospective analysis of patients of Glioblastoma multiforme treated with stem cell sparing intensity-modulated radiation therapy and nonstem cell sparing three-dimensional conformal radiation therapy: a single-institution experience. *J. Radiat. Cancer Res.* 9(3), 114–118 (2018).