RESEARCH ARTICLE

Comparison of Linear Accelerator and Helical Tomotherapy Plans for Glioblastoma Multiforme Patients

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Abstract

Background: Despite advances in radiotherapy, overall survival of glioblastoma multiforme (GBM) patients is still poor. Moreover dosimetrical analyses with these newer treatment methods are insufficient. The current study is aimed to compare intensity modulated radiation therapy (IMRT) linear accelerator (linac) and helical tomotherapy (HT) treatment plans for patients with prognostic aggressive brain tumors. Material and Methods: A total of 20 GBM patient plans were prospectively evaluated in both linac and HT planning systems. Plans are compared with respect to homogenity index, conformity index and organs at risk (OAR) sparing effects of the treatments. Results: Both treatment plans provided good results that can be applied to GBM patients but it was concluded that if the critical organs with relatively lower dose constraints are closer to the target region, HT for radiotherapeutical application could be preferred. Conclusion: Tomotherapy plans were superior to linear accelerator plans from the aspect of OAR sparing with slightly broader low dose ranges over the healthy tissues. In case a clinic has both of these IMRT systems, employment of HT is recommended based on the observed results and future re-irradiation strategies must be considered.

Keywords: Intensity modulated radiation therapy - GMB - dose comparison - linac - helical tomotherapy

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Introduction

Fourth grade gliomas or other named glioblastome multiforme (GBM) is the most aggressive brain tumor and it accounts for 12-15% of all brain tumors (Zach et al., 2009; Thilmann et al., 2001; Al-Mohammed, 2011; Manoharan et al., 2012). Due to its high potential of rapid progress, GBM is known to have lower survival rates and exhibits the worst prognosis (Mutlu et al., 2014; Chen et al., 2012; Doroudchi et al., 2013; Fuller et al., 2007).

Treatment process includes combination of surgery, radiotherapy and chemotherapy (Ge et al., 2013; Pashaki et al., 2014). Recent advances in both chemotherapy and radiotherapy have slightly improved the prognosis in patients with favourable prognostic factors (MacDonald et al., 2007). Radiotherapy has an important role in the treatment of brain tumors that should not be ignored. Technological advances have provided better radiotherapy techniques with improved target volume dose and lower critical organ doses. Intensity modulated radiation therapy (IMRT) is one of the highest-level treatment technique (Narayana et al., 2006; Shi et al., 2008; Zhu et al., 2012). IMRT reduces the morbidity and provides better local tumor control through giving higher doses to target volume and reducing toxicities by lowered critical organ doses (Al-Mohammed, 2011; Khoo et al., 1999; Williams, 2003; Hermanto et al., 2007). In radiotherapy of brain tumors IMRT, provides better dose conformity, homogenity and normal tissue sparing especially for irregulary shaped targets with multileaf collimators (Miwa et al., 2008; Mavroidis et al., 2007). Also, IMRT leads to higher doses and lowered late toxicity rates for GBM patients (Arnfield et al., 2000).

IMRT can be performed with different radiotherapy machines. Linac based IMRT and HT are also among the established radiotherapy methods. The linac based IMRT technique has been planned via multiple segmental portals. Many complex regulations have been made in treatment planning systems and linear accelerator machines; however, quality control parameters and frequencies have increased. Two methods have been developed to perform IMRT. One of them is called segmented multileaf collimator (sMLC) and the other one is known as dynamic multileaf collimator (dMLC) method (Arnfield et al., 2000). Step and shoot principle is applied on previously prescribed treatment angles in sMLC method while in machines with dMLC, irradiation continues with angle and/or table movements. Different irradiation portals can be choosen separately (5-7-9 fields or more) in linac based IMRT (Sheng et al., 2007). System will gain image

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guided radiation therapy (IGRT) capability with on-board megavoltage computerised tomography (MVCT).

Tomotherapy is a relatively a novel radiotherapy technique with increasing popularity (Kong and Hong, 2014; Blasi et al., 2011). The system has dynamic fast moving multileaf collimators that can move with each helical gantry rotations according to the table movement. Moreover the system exhibits IGRT capability with on-board MVCT (Murthy et al., 2010; Lian et al., 2008; Gupta et al., 2012). The binary multi-leaf collimator consists of 64 leaves which can be opened to project beamlets at 51 distinct angles for each rotation. Therefore; the binary multi-leaf collimator is able to produce 3264 possible beamlets in a single rotation around the patient.

The aim of this study is to compare linac based and helical tomotherapy IMRT plans with regards to target volume dose coverage, and critical organ sparing effects. The simultaneous integrated boost (SIB) technique with doses slightly higher than 2 Gy per fraction offers the advantages of shortening the treatment time and increasing the biologically equivalent dose to the tumor (Leclerc et al., 2013). Consequently SIB dose prescriptions were used for each patient in both linac based and helical tomotherapy IMRT plans.

Materials and Methods

Patient selection criterias and critical structure - target volume definitions

The prospective treatment plans of the twenty adult patients with GBM who had been operated and postoperatively treated in Erzurum, Regional Training and Research Hospital Radiation Oncology Clinic between April 2013- and October 2013 were included in the study. Two separate plans for HT and linac started after the patient accepted to participate in the study. Median age of the patients was 51 (range: 33-78). Patient and tumor characteristics are shown in Table 1. All patients were immobilised in supine position via three-clamp head and neck thermoplastic mask, scanned with 3 mm slice thickness through the region of interest in computerised tomography unit and images were transferred via network to workstation for contouring. The target and the critical organ volumes were outlined with Tomocon (TetramedTM, Slovak republic) workstation for helical tomotherapy and with Focal (ElektaTM) workstation for linear accelerators.

Gross tumor volume (GTV) was defined by the area of contrast enhancement observed on the CT scan or MRI. Two centimeter isometric margin was added to GTV in order to obtain clinical target volume (CTV) and 2.5 cm margin outlined around the CTV for defining planned target volume (PTV). Moreover the 2.5 cm margin to the GTV was used to define SIB volume. Our study population included a broad spectrum of tumor sizes, which ranged from 180 to 763 cm3 for initial PTVs, and 18 to 273 cm3 for boost PTVs Contoured organs at risk (OAR) included the whole brain minus PTV's, eyes, lenses, optic nerves, chiasma, pituitary gland, parotid glands, temporal lobes and brain stem. Outlined target volumes, non-target tissue, and OAR structures were transferred to both of the Tomotherapy and Linear accelerator planning systems via digital imaging and communications in medicine (DICOM) system.

Treatment planning

Linear accelerator based IMRT plans were made by 6 MV photon energy and the data was uploaded to Synergy model, CMS, XIO (Elekta AB, Stockholm, Sweden) planning system. The linear accelerator machine, which plans were prepared for, has 80 leaves with 1cm width at the isocenter. Treatment plans were created for 5 non-coplanar portals with 72, 135, 180, 236 and 286 angles.

Tomotherapy plans were made with IMRT technique in hi-Art HT planning system (Accuray Inc., Madison, USA). For all 20 cases, a field width of 2.5 cm, a pitch of 0.3, and a modulation factor of 2.0 was used during optimisation and dose calculation in order to achieve optimal plans. Direction block technique was used in some patient plans because of the dose constraints of critical organs.

Dose prescription

The simultaneous integrated boost (SIB) technique was adopted in all planning and delivery. Dose prescriptions in both linac and HT, IMRT plans were selected so that the planned target volume received 54 Gy (PTV54) and 60 Gy (PTV60=SIB) in 28 fractions. Dose constraints for OAR's were made according to normal tissue complication probability analyses (Kehwar, 2005; Emami et al,1991).

Plan evaluations

Linear accelerator and HT plans were evaluated qualitatively by visual inspection of dose washes in the axial, coronal and sagittal views, and quantitatively by using dose-volume histograms to define dose homogenity index, conformity index and OAR sparing.

According to the criteria of the International Commission on Radiation Units and Measurements 83 report: the near-maximum (D2%), near-minimum (D98%) and median (D50%) doses were used to asses the conformity index (CI), homogeneity index (HI) for plan evaluations (Servagi Vernat S et al., 2014). The evaluation indices described as follows:

$\underline{CI = VR / VT}$ Where VR is the volume of the reference isodose (95% of the prescribed dose) and VT is the volume of the target. The optimal value is 1.

$\underline{HI = D2\% - D98\% / D50\%}$ HI represents the homogeneity of the plan and optimal value is zero (ICRU report N0 83).

For the OARs, maximum and mean doses in Gy (Dmax and Dmean), appropriate organ specific dose/volume tresholds were recorded to estimate OAR sparing.

Statistical analyses

All statistical analyses were performed using SPSS for Windows, version 15.0 software (SPSS Inc., Chicago, IL, USA). Categorical variables were presented as counts and percents, numerical variables were presented as medians and standart deviations, and were compared using Wilcoxon test. A p-value lower than 0.05 was accepted as statistically significant in all analyses of this study.

Results

HT plans showed higher statistically significant near-minimum (D98%) and mean doses for SIB volume (PTV60) when compared with linac plans (p<0.0001). Furthermore CI and HI of the HT plans showed statistically significant superiority to linacs (p=0.016 and p=0.001) respectively. Dosimetric analyses for PTV50 showed statistically significant advantage for only D98% (p=0.005) (Table 2).

PRVof brainstem

HT allowed more sparing of PRV brain stem than linac plans. Mean, Dmean, D1/3 and D2/3 were significantly lower in case of HT (p<0.00, p<0.02 and p<0.04 respectively). Mean Dmax were higher than the planning objective in linac plans but no statistical significance was found between two plans. Total organ doses (D3/3) were very low without statistical significance (Table 3).

Optic chiasm

As for brainstem HT allowed more sparing of optic chiasm in terms of Dmean, D1/3, D2/3, D3/3 (p<0.00, p<0.00, p<0.01 and p<0.00 respectively). Mean Dmax was lower than linacs for tomotherapy but no statistical significance was observed (Table 3).

Optic nerves

HT showed statistically significant superiority for all dose comparisions. Dose plans did not exceed the planned objectives (Table 3).

Eyes and lenses

Mean Dmax, Dmean, D1/3 and D2/3 dose constraints were statistically significant between two plans, except total organ doses. No statistically significance was observed for lens dose parameters (Table 3). Both treatment plans were found to have similar efficiency and evaluated as acceptable for patient treatment.

Table 1. Patient and Tumour Characteristics

Characteristics	N	(%)
Sex		
Male	12	57.10
Female	9	42.90
Neurological symptoms		
Hemiplejia	6	28.60
Headache	6	28.60
Hemiparesis	4	19.00
Nausea, Vomiting	2	9.50
Cerebellar symptoms	2	9.50
Change in consciousness	1	4.80
Treatment protocol		
Adjuvant RT	8	38.10
Adjuvant KRT(temozolamid)	13	61.90
Anatomical localization		
Parietal	5	23.80
Temporal	4	19.00
Frontal	3	14.30
Occipital	3	14.30
Frontotemporal	3	14.30
Parietooccipital	2	9.50
Brainstem	1	4.80
Side of tumor localization		
Right	10	47.60
Left	9	42.90
Bilateral (central)	2	9.50

Table 2. Comparison of Mean Dosimetric Parameters for PTV60 and PTV50

	Helical Tomotherapy		Linear accelerator IMRT			
Variable	mean (Gy)	SD	mean (Gy)	SD	objective	P value
PTV60						
Dmax	62.90	1.50	63.10	3.30	-	0.52
Dmin	53.00	9.30	52.60	5.80	-	0.50
Dmean	60.90	0.60	59.60	0.80	-	0.00
D98%	60.00	0.20	58.30	1.70	60.0q	0.00
D2%	61.50	0.90	61.30	1.20	ALARA	0.54
CI	1.10	0.10	0.70	0.50	1.00	0.02
HI	0.00	0.00	0.10	0.10	0.00	0.00
PTV50						
Dmax	62.90	1.50	64.20	3.00	-	0.02
Dmin	35.30	11.60	42.80	11.70	-	0.01
Dmean	60.40	3.10	59.00	1.60	-	0.23
D98%	50.30	11.10	55.30	3.10	50.0q	0.01
D2%	61.20	2.50	61.20	1.20	ALARA	0.40

*Abreviations: Dmax: Maximum dose, Dmin: Minimum dose, Dmean : Mean dose, SD: Standart deviation; IMRT: intensity-modulated radiotherapy, D2%: dose of the 2% volume, D98%: dose of the 98% volume; HI: Homogenity index, CI: Conformity index, q: Quantec recommendation, ALARA: As Low As Reasonably Achievable

Discussion

Radiotherapy plays a major role in multimodality treatment of patients with GBM. In spite of newer radiation delivery techniques, it is unlikely to improve local control or overall survival for GBM patients compared with three dimentional conformal radiotherapy (3D-CRT) (Narayana et al., 2006; Fuller et al., 2013).

After 3D-CRT, IMRT consisted more radiation portals and as a result larger volume of the healthy tissues was exposed to low dose of radiation. IMRT provided better OAR sparing and PTV coverage. An earlier study concerning evaluation and comparison of 3D-CRT, linac IMRT, integrated boost and HT plans demonstrated that, HT plans provided more homogenous doses for both PTV (extensive and SIB) and were able to spare best small organs that usually lie close to the target volumes. The mean of the integral dose to the brain was significantly lower with integrated boost plan when compared to the others. They used the mean of the maximal dose to the OAR's with the various tratment plans as a surrogate to normal tissue sparing (Zach et al., 2009).

In the present manuscript HT provided better homogeneous doses for SIB volume but not for PTV 50. Mean of the maximal doses to each OAR were found higher for linac plans than HT plans with statistical significance, except brainstem planning risk volume (PRV). Mean maximum dose to brainstem (PRV) was also high in linac plan but there was no statistical significance.

The regimen of hypofractionated IMRT did not improve the time to disease progression or overall survival compared with historical experience using conventional fractionation (Floyd et al., 2004). Therfore, in this study usual doses are preferred in comparing IMRT plans.

There are few data regarding the comparison of

Table 3. Univariate Analysis of OAR doses of Patients with GBM (n=21)

Variable		Helical Tomotherapy Mean (Gy)	SD	Linear accelerator-IMRT Mean (Gy)	SD	Objective Quantec or TD5/5 (95% CI)[k]	p value
Brainstem (PRV)	Dmax	53.10	19.50	56.00	13.60	54.0[q]	0.08
	Dmean	12.70	13.40	27.40	12.30	ALARA	0.00
	D1/3	18.50	15.00	37.80	18.50	59.20 (56.10–62.31)[k]	0.02
	D2/3	4.60	10.50	11.20	15.70	55.15 (52.05-58.26)[k]	0.04
	D3/3	1.10	0.90	0.80	3.30	52.78 (49.67-55.89)[k]	0.07
Optic chiasm	Dmax	27.10	16.20	47.80	18.70	55.0[q]	0.10
	Dmean	12.00	11.50	37.60	16.20	ALARA	0.00
	D1/3	13.60	13.80	39.60	16.80	49.54 (37.54-61.54)[k]	0.00
	D2/3	10.60	18.90	35.40	15.70	49.54 (37.54-61.54)[k]	0.01
	D3/3	6.60	7.50	24.80	14.20	49.54 (37.54-61.54)[k]	0.00
Right optic nerve	Dmax	9.50	18.80	33.70	19.10	55.0[q]	0.00
	Dmean	9.00	12.10	20.10	14.20	ALARA	0.00
	D1/3	9.90	14.90	25.30	15.90	49.34 (46.06-52.62)[k]	0.00
	D2/3	8.20	9.80	18.70	60.40	49.34 (46.06-52.62)[k]	0.00
	D3/3	4.80	5.00	10.30	9.80	49.34 (46.06-52.62)[k]	0.00
Left optic nerve	Dmax	11.90	17.10	39.50	19.30	55.0[q]	0.00
	Dmean	8.30	9.30	26.80	14.80	ALARA	0.00
	D1/3	9.20	10.90	29.70	15.80	49.34 (46.06-52.62)[k]	0.00
	D2/3	6.40	7.90	20.30	14.10	49.34 (46.06-52.62)[k]	0.00
	D3/3	4.20	5.10	10.10	42.10	49.34 (46.06-52.62)[k]	0.00
Right lens	Dmax	4.70	4.10	6.00	2.60	ALARA	0.43
	Dmean	3.60	2.80	5.50	2.40	3.0[q]	0.57
	D1/3	4.00	3.00	5.60	2.40	6.762 (4.29-9.23)[k]	0.81
	D2/3	3.40	2.80	5.20	2.40	6.762 (4.294-9.229)[k]	0.57
	D3/3	3.00	2.40	4.50	2.40	6.762 (4.294-9.229)[k]	0.97
Left lens	Dmax	4.40	6.00	6.30	2.30	ALARA	0.22
	Dmean	3.40	4.60	4.90	2.10	3.0[q]	0.96
	D1/3	3.70	2.70	5.10	2.10	6.762 (4.29-9.23)[k]	0.88
	D2/3	3.50	4.60	4.70	2.10	6.762 (4.294-9.229)[k]	0.65
	D3/3	2.70	3.80	3.90	2.10	6.762 (4.294-9.229)[k]	0.85
Right eye	Dmax	11.20	11.50	25.80	18.50	20.0[q]	0.00
	Dmean	4.50	3.50	8.70	5.30	ALARA	0.00
	D1/3	5.10	7.20	9.10	6.90	44.67 (43.04-46.29)[k]	0.01
	D2/3	3.70	3.00	5.80	3.40	44.67 (43.04-46.29)[k]	0.01
	D3/3	2.20	2.10	4.00	2.10	44.67 (43.04-46.29)[k]	0.77
Left eye	Dmax	11.60	13.90	20.40	19.50	20.0[q]	0.00
	Dmean	5.00	5.10	8.80	5.30	ALARA	0.00
	D1/3	5.90	6.10	9.90	6.90	44.67 (43.04-46.29)[k]	0.00
	D2/3	3.60	4.50	7.20	3.40	44.67 (43.04-46.29)[k]	0.15
	D3/3	2.10	2.70	3.00	2.00	44.67 (43.04-46.29)[k]	0.93

*Abreviations: Dmax: maximum dose, Dmean : mean dose, SD: Standart deviation, IMRT: intensity-modulated radiotherapy, PRV: Planning organ at risk volume, D1/3: 33% of the volume that recieved prescribed dose, D2/3: 66% of the volume that recieved prescribed dose, D3/3: 100% of the volume that recieved prescribed dose, ALARA: As Low As Reasonably Achievable; TD5/5 (95% CI)[k]- 5% probability of severe sequelae in five years (in Keshwar recommendation); [q]Quantec recommendation, k: Keshwar recommendation

treatment plans between HT and linear accelerator IMRT plans. Cao et al, evaluated the plan qualities of ten patients provided by intensity-modulated arc therapy (IMAT) and HT. They concluded that, IMAT can provide plan qualities comparable to that of HT in most of the cases. Their ten cases were chosen to cover a range of body sites (Cao et al, 2007).

Chen et al. (2013) compared the effect of IMRT versus 3D-CRT on clinical outcomes of the patients with GBM and concluded that, the lack of survival benefit and increased costs of IMRT needs to be carefully rationalised in the treatment of GBM. Their sixteen patients (29.6%) was refused to undergo adjuvant chemotherapy because of poor economic condition or intolerable side effects. There was no information about the used devices in the IMRT planning and treatment of the patients.

Basic mentality for the radiation therapy is; if one can achieve lower toxicity rates, can give higher doses to intractable tumors and pretreatment planning evaluation is the mainstay for the radiotherapeutic approach. Meticulous planning with appropriate dose comparisons are mandatory for the patients. The dose comparisons also relies on the operator. Different operators may weight dose constraints differently for both tumor and OARs. Moreover close proximity of the OARs with low dose constraints are important determinants of the planning decision (Sheng et al., 2007). As a result individualised or adaptive therapies with higher doses seems mandatory

for the GBM treatment.

Almost all patients with GBM underwent irradiation as a part of the initial treatment and it is possible to apply both linac IMRT and HT radiotherapy plans on patients. But, when re-irradiations are considered, OAR dose constraints gains more importance (Koga and Saito, 2012). Dose constraints of the OAR should be carefully evaluated in the initial irradiation plans and HT seems to have better plans from the aspect of OAR sparing effect.

In conclusion, it is unlikely to improve local control or overall survival for GBM patients with the newer radiation delivery techniques. Therefore, different fractionation schemes or higher radiation doses and better planning methods are seems mandatory. Moreover, rigorous planning for initial irradiation can give future irradiation chance to the patients. In the light of the recent studies, HT is preferable in GBM treatment; however patient-specific adaptive therapies are also required in order to improve survival rates.

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