Pol J Med Phys Eng 2011;17(2):75-84
PL ISSN 1425-4689
doi: 10.2478/v10013-011-0008-1
website: http://www.pjmpe.waw.pl

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Dosimetric comparison of three dimensional conformal radiotherapy and intensity modulated radiotherapy in high grade gliomas

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Treatment of high-grade gliomas continues to be frustrating for the clinician as the medial survival stands at a dismal 14.5 months for glioblastoma multiforme (GBM) with the current standard of care. Given the high dose and generous margins required to be irradiated, three dimensional conformal radiotherapy (3DCRT) has become standard practice. Radiation dose escalation beyond 60 Gy, by means of stereotactic or intensity modulated radiotherapy (IMRT) boost, has not yielded clinically significant benefits in terms of local control or survival. At the same time, the potential of IMRT to spare normal tissues such as the brain stem and the optic apparatus makes it an attractive tool for modern radiation oncologists in seeking to improve post-radiotherapy quality of life. At our centre, we have been treating a large number of cases of high grade glioma with 3DCRT and IMRT for the last several years. The present study has been an effort to understand any potential benefits that IMRT, even without dose escalation, can offer.

Introduction

Glioblastoma multiforme (GBM) is the most common primary malignant brain tumour and the commonest brain tumour overall today. Treatment of high-grade gliomas continues to be

frustrating for the clinician as the medial survival stands at a dismal 14.5 months for glioblastoma multiforme (GBM) with the current standard of care, surgery followed by external beam radiotherapy of 60 Gy by conventional fractionation with concurrent and adjuvant Temozolamide [1]. Given the high dose and generous margins required to be irradiated for high grade gliomas, three dimensional conformal radiotherapy (3DCRT), with multiple coplanar/ non-coplanar beams shaped by multi-leaf collimators (MLCs), have become standard practice. Radiation dose escalation beyond 60 Gy by means of stereotactic or intensity modulated radiotherapy (IMRT) boost to the gross tumor as seen on preoperative MRI or to the tumour bed, has not yielded clinically significant benefits in terms of local control or survival [2], in comparison to other sites such as cancer of the head and neck [3] or prostate [4]. At the same time, the potential of IMRT to spare normal tissues such as the brain stem and the optic apparatus makes it an attractive tool for modern day radiation oncologists in seeking to improve post-radiotherapy quality of life. Unfortunately, dosimetric and clinical data on IMRT for GBMs and other high-grade gliomas is sparse. At our centre, we have been treating a large number of cases of high grade glioma with 3DCRT and IMRT for the last several years. Naturally treatment modalities need to be individualised depending on specific tumor locations and proximity to critical normal structures, but an overall analysis of treatment techniques is still very much called for. The present study has been a natural result of our experience and our curiosity in understanding any potential benefits that IMRT, even without dose escalation, can offer to the patient. In this study we shall be analysing the dosimetric advantages of IMRT while the clinical results will be discussed at a later time.

Materials and Methods

Twenty five patients of biopsy-proven high grade glioma (glioblastoma multiformae/ gliosarcoma/ anaplastic astrocytoma/ anaplastic oligodendroglioma) in a variety of locations were included in the study.

All patients were virtually simulated. During simulation, all patients were immobilized using 3-clamp thermoplastic mould (Orfit) using normal neck rest or neck flexion, according to location of the tumor and 3mm CT slices were acquired after injection of intravenous contrast. In most patients, MRI with Gadolinium contrast was also acquired and fused with the CT images.

In patients who had undergone biopsy or subtotal resection, the clinical target volume (CTV) was contoured as the contrast enhancing area as seen on pre-intervention MRI with a

2 cm isotropic margin, which was routinely edited only from the cranial bone and extracranial structures. In some special cases, where the lesion was in close proximity to the brain stem or optic apparatus, the CTV was edited off these structures. The planning target volume (PTV) included the CTV with a 0.5 cm isotropic margin, which was edited only to keep it within the external contour, with a 0.3 cm margin for accurate dosimetry on the treatment planning system (TPS).

All patients were then planned on the PLATO Sunrise (v.2.77) planning system (Nucletron BV) using 3-5 beams, both coplanar and non-coplanar, as indicated, with 6 MV photons. For each patient, two plans were generated-the best achievable 3DCRT plan and the best achievable IMRT plan, keeping in mind both the target coverage and normal tissue tolerance. It was endeavoured to keep the PTV coverage between 95% and 107% of the prescribed dose, as per ICRU conventions. The prescribed dose was 59.4-60 Gy/30-33# at 1.8-2 Gy/# to the PTV.

Subsequently a dosimetric comparison was done, to evaluate differences in both target coverage and normal tissue sparing. For the former, dose volume histograms (DVHs) of the plans were analysed according to D95 (dose received by 95% of the PTV), maximum, minimum and average dose to the PTV.

Dose homogeneity within the PTV was also assessed using the D20 (dose received by 20% of the PTV), the D5% (dose received by 5% of the PTV) and the inhomogeneity coefficient [IC=(Dose received by 5% of the PTV-Dose received by 95% of the PTV)/Average PTV Dose]. [5]

For evaluation of normal tissue sparing, we evaluated dose received by brain stem (1%), optic chiasm (1%), optic nerves (1%), eyes (average), lens (maximum), pituitary (maximum), temporal lobes (maximum), normal brain (1/3, 2/3 and whole) and spinal cord (1%).

Conformity was assessed using the Conformity Index of Paddick et al [6], which is calculated as follows: CI= (PTV volume x Prescribed Isodose Volume)/ Volume of PTV receiving the Prescribed Isodose Volume.

Statistical analysis was done using the SPSS software (version 13.0). The Wilcoxon matched pairs signed rank test was used for comparing the 2 sets of plans.

Results

Descriptive statistics (Table 1)

Most of the patients (19/25 or 76%) selected for the study had Grade IV glioma while the rest (6/25 or 24%) had Grade III glioma.

The most common site of tumour was the temporoparietal region (13/25 or 52%), while the next commonest was the frontal region (8/25 or 32%), followed by the occipital region (2/25 or 8%) and cerebellar region (2/25 or 8%).

Tumours were uniformly distributed with respect to left and right sides (13/25 or 52% vs 11/25 or 44% respectively) with only a single centrally occurring tumour.

All patients had subtotally resected tumour with no examples of biopsy-alone or total resection.

PTV volume ranged from 144.9cc-738.7cc with a median of 278.8cc.

Table 1. Descriptive statistics

		Number (%)
Grade	Grade III Grade IV	6 (24%) 19 (76%)
Lobe	Frontal Temporo-parietal Occipital Cerebellar	8 (32%) 13 (52%) 2 (8%) 2 (8%)
Location	Left Right Central	13 (52%) 11 (44%) 1 (4%)
Extent of resection	Biopsy Subtotal Total	0 (0%) 25 (100%) 0 (0%)
PTV volume (cc)	Range Median	144.9 cc - 738.7 cc 278.8 cc

Dosimetric analysis

PTV coverage was not significantly improved by IMRT (p=0.788 for PTV 95% although p‹0.001 for PTV average). On the other hand, maximum and minimum doses to the PTV were significantly different with IMRT (p‹0.001 for both) (Table 2).

Table 2. PTV coverage

Parameter	3DCRT Mean (cGy)/ (Standard Deviation)	IMRT Mean (cGy)/ (Standard Deviation)	P
D95% (cGy)	5861.76 (164.12)	5859.92 (167.62)	0.788
D20% (cGy)	6187.72 (116.03)	6373.12 (125.78)	‹0.001
D5% (cGy)	6265.56 (94.96)	6530.64 (106)	‹0.001
PTVaverage (cGy)	6085.12 (124.4)	6225.44 (75.07)	‹0.001
PTVmax (cGy)	6389.08 (103.14)	6807.92 (177.4)	‹0.001
PTVmin (cGy)	4999.2 (776.3)	4396.56 (526.12)	‹0.001

D95%= Dose received by 95% of the PTV

D20%= Dose received by 20% of the PTV

D5%= Dose received by 5% of the PTV

PTVaverage= Average dose to the PTV

PTVmax= Maximum dose to the PTV

PTVmin= Minimum dose to the PTV

Dose homogeneity within the PTV was significantly better for 3DCRT (p‹0.001 for PTV 5%, p‹0.001 for PTV20%). As a result, the inhomogeneity coefficient (IC) was significantly superior with 3DCRT than with IMRT (p‹0.001). On the other hand, the conformality of the prescribed dose was significantly improved by IMRT (p‹0.001 for conformity index) (Table 3).

Table 3. Dose Homogeneity and Conformity

Parameter	3DCRT Mean / (Standard Deviation)	IMRT Mean/ (Standard Deviation)	p
Inhomogeneity Coefficient (IC)	6.68 (2.58)	10.76 (3.37)	‹0.001*
Conformity Index (CI)	0.47 (0.14)	0.74 (0.08)	‹0.001

***=** favouring 3D CRT

As far as OAR sparing is concerned, the doses to the optic apparatus and brain stem were not significantly different across all sites in the brain, except for a significant reduction of the optic chiasm dose (p=0.02) with IMRT (Table 4). On sub site analysis, it was found that IMRT was able to significantly improve the optic chiasm sparing only for temporo-parietal tumours (p=0.039), whereas for other sites, there was no significant difference between the 2 arms (p= 0.069, 0.18, 0.65 for frontal, occipital and cerebellar tumours, respectively) (Table 4).

Table 4. OAR sparing

Parameter	3DCRT Mean (cGy)/ (Standard Deviation)	IMRT Mean (cGy)/ (Standard Deviation)	p
R Optic nv. 1% (cGy)	2315.24 (2107.96)	2030.28 (1815.4)	0.076
L Optic nv. 1% (cGy)	2067.88 (1991.74)	1688.8 (1737.36)	0.054
R Eye avg. (cGy)	728.72 (703.63)	1015.04 (861.12)	0.088
L Eye avg (cGy)	690.64 (761.88)	712.84 (482)	0.716
Optic chiasm 1% (cGy)	3591.44 (2399.34)	2945.32 (2002.66)	0.002
Brain stem 1% cGy)	4145.8 (2356.9)	3739.24 (2262.07)	0.006

Doses to the whole brain were significantly reduced, rather than increased with IMRT (p‹0.001 for dose to 33% of the whole brain and p=0.001 for average whole brain dose) (Table 5).

Table 5. Whole Brain Dose

Parameter	3DCRT Mean (cGy)/ (Standard Deviation)	IMRT Mean (cGy)/ (Standard Deviation)	p
Whole Brain 33% (cGy)	4525.62 (1469.32)	3964.67 (1430)	‹0.001
Whole Brain 66% (cGy)	1627.83 (1580.63)	1441.83 (1233.62)	0.304
Whole Brain avg (cGy)	3196.04 (977.3)	2887.96 (1016)	0.001

Discussion

Following its success in cancers of the head and neck and prostate, and because of its increasing availability, IMRT is nowadays being used more and more in the management of high-grade gliomas (anaplastic astrocytoma, anaplastic oligodendroglioma, glioblastoma and gliosarcoma). Though dose escalation beyond conventionally delivered doses has not proved

beneficial in terms of local control or overall survival in high grade gliomas, IMRT and 3DCRT hold considerable promise as far as OAR sparing is concerned.

In a retrospective analysis of 58 consecutive patients of high-grade glioma treated with IMRT at Memorial Sloan Kettering Cancer Centre between 2001 and 2003, Narayan et al. [7] did not find any improvement in either progression –f ree survival or overall survival over historical data with 3DCRT (albeit this was in the pre-Temozolamide era). Even dosimetrically, in comparison to 3DCRT, IMRT did not produce any significant improvement in PTV coverage, with no differences seen in the PTV maximum dose, mean dose or D95 coverage [7]. At the same time, IMRT was found to significantly reduce the brain stem dose while the maximum doses to the optic apparatus structures were also much lower. Importantly, the IMRT plan did not produce any increase in the normal brain dose, in-fact, the volume of normal brain irradiated was significantly less with IMRT, with volumes receiving 18 Gy and 24 Gyreduced by 7% and 8%, respectively, compared to 3DCRT.

In order to explain the clinical outcome, the authors concluded that we are yet to find the optimal doses, volumes and fractionation schedules for high grade gliomas. As far as dosimetry was concerned, the authors pointed out that 3DCRT is excellent in achieving adequate coverage and homogeneity for the volumes typically irradiated in high-grade gliomas, with spherical or cylindrical targets without too many concavities unlike say, head and neck or prostate cancers, where the targets are always concave and irregular shaped.

In another dosimetric study at MD Anderson Cancer Centre , Hermanto et al. [8] compared IMRT and 3DCRT plans for a group of 20 patients of high-grade glioma treated between 2004-2005 and found no significant differences in the DVH parameters of PTV coverage, including inhomogeneity coefficient (IC). IMRT was able to reduce non-target dose to critical structures like brainstem and optic apparatus by significant amounts and also reduced total integral dose by 7-10%. IMRT was found to be significantly better in conforming the prescribed dose to the PTV ($p<0.01$) and was also able to control the spread of the low doses, especially at 5 and 10 Gy, and does not significantly increase the 0-5 Gy low dose volume.

Other studies have looked at IMRT for escalating dose to the GTV. In a study by Chan et al. [9] at MSKCC, 5 consecutive patients were planned for both 3DCRT using 3 noncoplanar fields and IMRT. In both arms, a dose of 59.4 Gy was prescribed to the PTV, while the IMRT plan included a simultaneous boost to the GTV up to 70 Gy. DVH analysis showed that while dose to the PTV was comparable in the 2 arms, the GTV doses (maximum, minimum and average) were about 10% higher for IMRT than for 3DCRT. On the other hand, while OAR doses in general were comparable across the 2 arms, the IMRT plans allowed significantly

superior sparing of the normal brain and also prevented occurrence of hot spots outside the PTV. The authors felt that the ability to deliver higher doses to the GTV and improved sparing of the normal brain were important advantages of IMRT.

Similarly, MacDonald et al, in their study [10] compared 3DCRT and IMRT plans for 20 patients using a phased plan, initially delivering 45 Gy to the whole PTV, followed by boost to 59.4 Gy to the coned-down PTV (GTV with margin). Dosimetric analysis revealed superior target coverage with IMRT with statistically significant increased maximum and minimum PTV doses as well as significantly increased D100. The IMRT plans also significantly reduced doses to the uninvolved brain, brain stem and optic apparatus. The TCP (Tumour Control Probability) and NTCP (Normal Tissue Complication Probability) scores were also significantly superior for IMRT as compared to 3DCRT.

In our study, dose escalation to the GTV was not attempted, and a uniform dose was prescribed to the entire PTV. The PTV coverage with IMRT is not superior to 3DCRT in terms of overall tumour coverage (PTV maximum, minimum and average doses as well as D95 coverage), hence use of IMRT may not significantly affect the local control rates. At the same time, IMRT produces significant dose inhomogeneity within the PTV as well. However, by achieving steep dose fall-off outside the PTV, IMRT makes the dose distribution more conformal. This suggests that both acute and late toxicities should be significantly reduced with IMRT, which should translate into superior post-radiotherapy quality of life, superior neurocognitive status and perhaps superior tumour control. It was also confirmed that with specific tumour locations and shapes, though not in all, IMRT is able to significantly improve the sparing of critical structures, such as the brain stem and optic apparatus.

The inherent inhomogeneity of IMRT might be utilized to escalate dose to the GTV using the simultaneous integrated boost technique. Iuchi et al. [11] at the Chiba Cancer Center treated 25 malignant astrocytoma (MA) patients using three layered planning target volumes (PTVs). PTV-1 was the area of enhanced lesion with 5 mm margin; PTV-2 was the area with 15 mm margin surrounding the PTV-1; PTV-3 was the area of perifocal edema. Irradiation was performed in 8 fractions, and only the dose for PTV-1 was escalated from 48 Gy to 68 Gy while maintaining the dose for PTV-2 (40 Gy) and PTV-3 (32 Gy). The clinical outcome of IMRT was compared with 60 MA patients treated by conventional external beam irradiation (EBI). The progression-free survival of patients in the IMRT group was significantly longer than that in the EBI group ($p < 0.0001$). No distant failure was observed in both groups. In the IMRT group, dissemination was the most frequent cause of death (70%). The overall survival of patients in the IMRT group was better than that in the EBI group ($p = 0.043$).

IMRT also has the potential to safely hypofractionate and thereby decrease the radiotherapy treatment duration. Recently, Valerie Panet-Raymond et al [12] reported their results in 30 GBM patients treated using a dose of 60 Gy and 40 Gy delivered in 20 fractions prescribed to the periphery of the gross tumour volume and planning target volume, respectively with concurrent and adjuvant temozolomide. Their results showed that hypo-IMRT with concomitant and adjuvant TMZ is well tolerated with a useful 2-week shortening of radiotherapy. Despite a high number of patients with poor prognostic features (74.3% recursive partitioning analysis class V or VI), the median survival was comparable to that after standard radiotherapy fractionation schedules plus TMZ.

Conclusions

We can conclude from our study that IMRT helps to improve conformality without having an impact on tumour coverage and also at the expense of more dose inhomogeneity within the PTV. Dose to the uninvolved brain was found to be significantly less in case of IMRT as compared to 3DCRT , even though we had expected the converse .Overall however ,except for situations where the shape of the PTV or the location mandates usage of IMRT in order to better cover concave shaped volumes , usage of IMRT does not impart a significant advantage in terms of OAR sparing or potential for dose escalation.

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