Effective comparative indices for complex brain radiotherapy involving overlapping target and normal tissue structures in glioblastoma multiforme patients: VMAT vs 3D conformal

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INTRODUCTION

- Dosimetric indices are often used for radiotherapy treatment plans evaluation; however, these indices do not account for positional information in the volumes considered and their implications on the relevant clinical end points.
- Therefore the tumour control probability (TCP) as well as the normal tissue complication probability (NTCP) should also be taken into consideration.
- This is particularly important in brain radiotherapy, a situation where there is a potential high level of dose heterogeneity in normal structures and/or where tumour coverage has to be compromised [1].
- This study is concerned with the effectiveness of physical and radiobiological brain radiotherapy plan quality metrics considering target and normal structure proximity/overlap.
- Based on comparisons between three-dimensional conformal radiotherapy (3D-CRT) and volumetric modulated arc therapy (VMAT) and using both physical and radiobiological parameters, we investigated if the dosimetric superiority of a plan can be directly translated as superiority of NTCP and TCP.

MATERIALS & METHODS

- Retrospective data from 56 3D-CRT (XiO, v.62, Elekta Inc) and 33 VMAT (Eclipse, v.10.0.28, Varian) glioblastoma multiforme (GBM) plans (Rx: 60 Gy/30 fr) were analysed (VMAT sample: all data available). Calculation differences between the two algorithms employed (Superposition Convolution vs Anisotropic Analytic Algorithm) do not impact the study as no significant difference has been reported in homogeneous cases such as in the brain [2].
- Mean, minimum and maximum doses were calculated for planning target volumes (PTV) and principal organs-at-risk (OAR) (brainstem, optic nerves and optic chiasm). Target coverage with the 95% isodose (V95), conformity (CI) and homogeneity (HI) indices were also evaluated.
- TCP, NTCP and equivalent uniform dose (EUD) were calculated in *BioSuite* using published Linear-Quadratic and Lyman-Kutcher-Burman model parameters [3-8]. Radiobiological values are considered relative due to the wide variability in published parameters.
- Sample stratification based on target-OAR proximity:

	3D-CRT	VMAT
"overlap": target overlaps with any OAR	25	18
"adjacency": target-OAR separation ≤ 0.5 cm	13	11
"no overlap": target-OAR separation > 0.5 cm	18	4

RESULTS & DISCUSSION

Dosimetric Evaluation

Targets

"no overlap"/"adjacency": V95 and HI similar

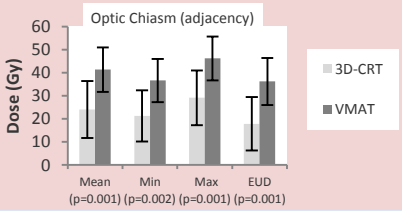
"overlap":
- V95: 95.9 ± 2.6 % (VMAT) vs 86.7 ± 10.7 % (3D-CRT) ($p \leq 0.001$)
- HI: 13.3 ± 3.0 (VMAT) vs 17.0 ± 4.4 (3D-CRT)($p < 0.05$)

all cases: CI: 1.0 ± 0.1 (VMAT) vs 1.1 ± 0.2 to 1.4 ± 0.1 (3D-CRT) ($p \leq 0.001$)

Optic nerves
- **"no overlap"**: similar D_{mean}, EUD and D_{max}
- **"adjacency"**: less sparing with VMAT (laterality not considered)
- **"overlap"**: similar results

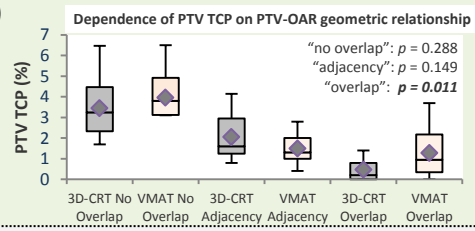
Brainstem
- **"no overlap"/"adjacency":** similar results
- **"overlap":** D_{mean}, D_{min} and EUD significantly lower for VMAT ($p < 0.05$)

Optic Chiasm
- **"no overlap"/"overlap":** similar results
- **"adjacency":** better spared in 3D-CRT



Radiobiological Evaluation

Targets (TCP)



Box lines: bottom, middle and top represent the 1st quartile, median and 3rd quartile. Rhombi: mean values. Whiskers: extend from the 1st and 3rd quartiles to the smallest and largest non-outliers respectively.

A range of α/β values was considered for the PTV to account for the wide variability in published parameters. Values presented correspond to α/β = 5.6 which yields a higher rate of non-zero TCP values and facilitates comparison when compared to other quoted values of 8 – 8.3.

OAR (NTCP)

"no overlap"/"adjacency": differences statistically insignificant for all OAR

"overlap":
- optic nerves : similar for 3D-CRT/VMAT (laterality not considered)
- optic chiasm: 2.1 ± 2.4 % (3D-CRT) vs 0.9 ± 1.3 % (VMAT) ($p < 0.05$)
- brainstem : 36 ± 8.8 % (3D-CRT) vs 27.4 ± 11.8 % (VMAT) ($p < 0.05$)

CONCLUSION

VMAT was dosimetrically substantially superior to 3D-CRT in terms of target mean dose, V95 coverage and homogeneity for cases of tumour/OAR overlap while differences between the two techniques were insignificant for less challenging cases. Significantly higher PTV TCP and significantly lower NTCP were achieved for the optic chiasm and brainstem with VMAT in cases of tumour/OAR overlap while similar TCP/NTCP values were obtained with both techniques for all structures for the less challenging cases.

The radiobiological based observations generally correlated with observations based on **dosimetric metrics** implying that the latter **may be adequate representatives of biological effectiveness in similar clinical cases.** Addressing the question of how directly the dosimetric superiority of a plan can be translated as superiority at a biological level is rather challenging; for example, the PTV TCP increase with VMAT observed in the "overlap" case is 0.8% which could be considered disproportional to the 9% gain in tumour V95 coverage with VMAT. These issues will be addressed in a further study using appropriate fitting of both types of metrics with patient outcome data in appropriately stratified samples, factoring in all possible confounders.

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