DOSIMETRIC AND CLINICAL RESULTS WITH VOLUMETRIC MODULATED RADIOTHERAPY FOR GLIOBLASTOMA MULTIFORME: OUR EXPERIENCE

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ABSTRACT

Objective. To evaluate the dosimetric and clinical results with volumetric modulated arc therapy (VMAT) for glioblastoma multiforme (GBM) treatment in our institution.
Material and methods. Thirty GBM patients that underwent adjuvant VMAT radiotherapy between January 2017 and June 2019, were assessed considering treatment plan performance and survival data. Means of dose-volume histograms (DVHs) for both planning target volume (PTV) and organs at risk (OARs) were used for the quantitative plan evaluation.
Results. A median progression free survival (PFS) of 6.3 months (95%CI: 4.1-8.5) and median overall survival (OS) of 15 months (95%CI: 7.9-22.2) months were recorded. PTV scored a V95% of 97.7±2%, a CI of 0.98±0.02 and a HI of 0.08±0.03. V18Gy for the normal brain was 51.1±17.1%. Treatment plans yielded a number of 517±112.7 monitor units per fraction.
Conclusion. We document our radiotherapy practice since VMAT implementation with treatment results consistent with international literature.

Keywords: glioblastoma multiforme, volumetric modulated arc therapy, dosimetry, survival

INTRODUCTION

Glioblastoma multiforme (GBM) is considered the deathliest malignant glioma in adults with a median survival of 15 months and 2-year survival of 27% (1). The standard multimodality treatment since Stupp et al. (2) study involves maximal safe resection, followed by concurrent alkylating agent Temozolomide chemoradiotherapy and maintenance chemotherapy.

Near-complete ablation is correlated with a better outcome (3,4), but it is often not feasible due to surgery-related risks which enhance the importance of the adjuvant local treatment.

Modern radiotherapy techniques aim to increase tumor control while reducing irradiation to normal tissues. On this note, technology like volumetric-modulated arc therapy (VMAT) is increasingly popular due to the rapidity of treatment delivery and better planning target volume (PTV) dose distribution and organs at risk (OARs) avoidance, when compared to tri-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT) (5–7). In GBM patients, this may be explicitly useful, given the central nervous system (CNS) anatomical features, such as the proximity and sometimes the overlapping of the PTV over the radiosensitive normal tissues like brainstem, spinal cord, eyes, lenses, optic nerves, optic chiasm, pituitary gland and healthy brain as well.

Nevertheless, even with aggressive multimodality therapy, most patients experience local failure

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(8) and require individualized second-line treatment. VMAT can be used for salvage reirradiation while maintaining a satisfactory neurological status (9).

The aim of this study was to report our experience considering plan performance and clinical results of GBM patients treated since the availability of VMAT in our institution. Relevant dosimetric parameters for PTV and OARs and survival outcomes in terms of progression free survival (PFS) and overall survival (OS) were analyzed and compared with previously published data.

MATERIAL AND METHODS

We analyzed thirty consecutive GBM patients 50 years of age or over, treated with adjuvant volumetric modulated radiotherapy in Gral Medical Clinic between January 2017 and June 2019. This study was approved by the Hospital's ethical board and all personal medical data were accessed and handled according to the institutional policy and national legislation. Patient characteristics are detailed in Table 1.

Patients underwent computed tomography (CT) simulation in the supine position with a custom-made thermoplastic face mask (Figure 1). Images were integrated into the Monaco version 5.10 (Elekta AB, Stockholm, Sweden) treatment planning system (TPS) and coregistered with the postresection magnetic resonance examination. The clinical target volume (CTV) consisted of a 2 cm isotropic margin of the gross tumor volume (GTV), representing the surgical cavity and any residual disease delimited on the T1-weighted MRI (10). Planning target volume (PTV) encompassed the CTV plus a 0.5 cm circumferential extension. Normal tissue delineation comprised the brainstem, spinal cord, eyes, lenses, optic nerves, optic chiasm, pituitary gland and healthy brain, as the whole brain minus the PTV.

The planning objectives included for PTV a minimum dose (D_{min}) of more than 95% and a maximum dose (D_{max}) of less than 107% of the prescribed dose and for OARs the following: D_{max} for brainstem and optic nerves/chiasm was limited to 54 Gy, D_{max} for spinal cord, eyes and pituitary gland was limited to 45 Gy and D_{max} for lenses was limited to 7Gy. The prescription dose was either 59.4 Gy in 33 fractions (in two cases) or standard 60 Gy in 30 fractions.

All plans were designed on Monaco TPS by utilizing 6 Mega Voltage (MV) photon beams for Versa HD (Elekta AB, Stockholm, Sweden) linac. A 3 mm calculation grid was applied to perform dose computation by using the X-ray voxel Monte Carlo (XVMC) algorithm. The arc pattern used in treatment planning consisted of single or multiple partial or full arcs with a coplanar and non-coplanar arrangement, according to a personalized plan optimization. Whenever possible, there was an attempt to use a limited number of arcs (as detailed in Table 2) in consideration of plan complexity and normal brain exposure to low dose levels.

TABLE 1. *Patient characteristics*

Description	Number (N=30)
Gender (n)	
– Male	19
– Female	11
Age (y)	
– Median	61
– Range	50-72
Tumor location – lobe (n)	
– Temporal	9
– Parieto-Occipital	6
– Parietal	3
– Frontal – Temporo-Parietal	5 3
– Other	4
Tumor side – hemisphere (n)	
– Left	20
– Right	9
– Bilateral	1
The extent of surgical resection (n)	
– Biopsy	2
– Subtotal resection	20
– Total/ near total tumor resection	8
Karnofsky performance status (%)	
– Median	70
– Range	60-80

The dosimetric analysis of treatment plans for the PTV included: near-maximum absorbed dose ($D_{2\%}$ – dose delivered to 2% of PTV), target coverage ($V_{95\%}$ – volume enclosed by at least 95% of the prescribed dose), homogeneity index defined by the equation $(D_{2\%} – D_{98\%})/D_{50\%}$ (11) and conformity index defined as the ratio between the 95% isodose volume ($V_{95\%}$) and the target volume (TV) (12). Critical structures analysis comprised of maximum normal tissue absorbed dose for all OARs and V_{18Gy}

(percentage of volume receiving 18 Gy) for the normal brain. Monitor units (MUs) were also recorded. Mean values and standard deviation of the selected parameters were computed and reported.

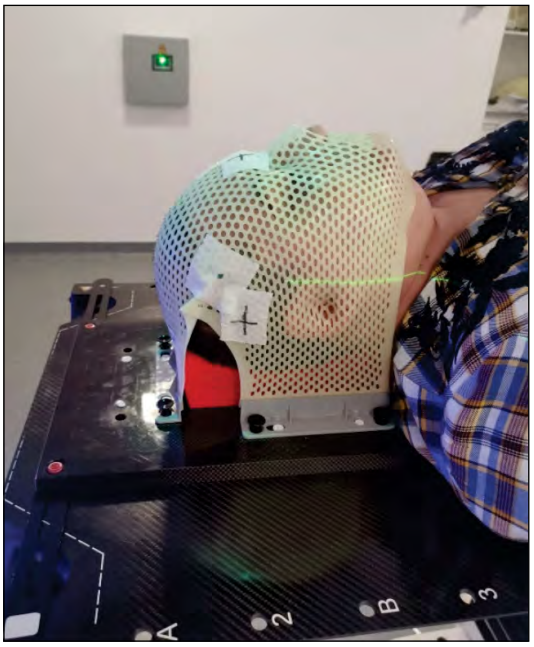


Figure 1. *Patient immobilization with a custom made thermoplastic mask during CT simulation for the radiotherapy procedure.*

The standard clinical assessment performed prior radiotherapy treatment included medical history, physical examination, performance status evaluation and complete blood count. Toxicity during radiotherapy treatment was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (13). Post-surgical MRI was set as the radiographic response baseline, whereas follow-up MRIs were performed 4 weeks after treatment completion and every 3 months subsequently.

TABLE 2*. Arc patterns*

Parameter	No. of patients
Arc description (n)	
– 1 partial arc	6
– 2 partial arcs	14
– 1 full arc	4
– > 1 full arc	6
Couch orientation (n)	
– Coplanar Arrangements	21
– Non-coplanar Arrangements	9
Collimator (degrees)	
– 10/ 10 and 350	28
– 30/30 and 330	2

The date of the diagnosis was considered as the date of the initial surgery, while the date of progression was defined as the date of the first progression according to Response Assessment in Neuro-Oncology (RANO) (14) criteria on the magnetic resonance (MRI) follow-up examination.

Overall survival (OS) was calculated as the interval between the date of the diagnosis and death or last follow-up for surviving patients, while progression-free survival was considered the interval between the date of diagnosis and progression or death. Kaplan-Meier method was used to calculate both OS and PFS.

The statistical analysis was conducted by using IBM SPSS Statistics for Windows version 23 (IBM Corp., Armonk, N.Y., USA) software.

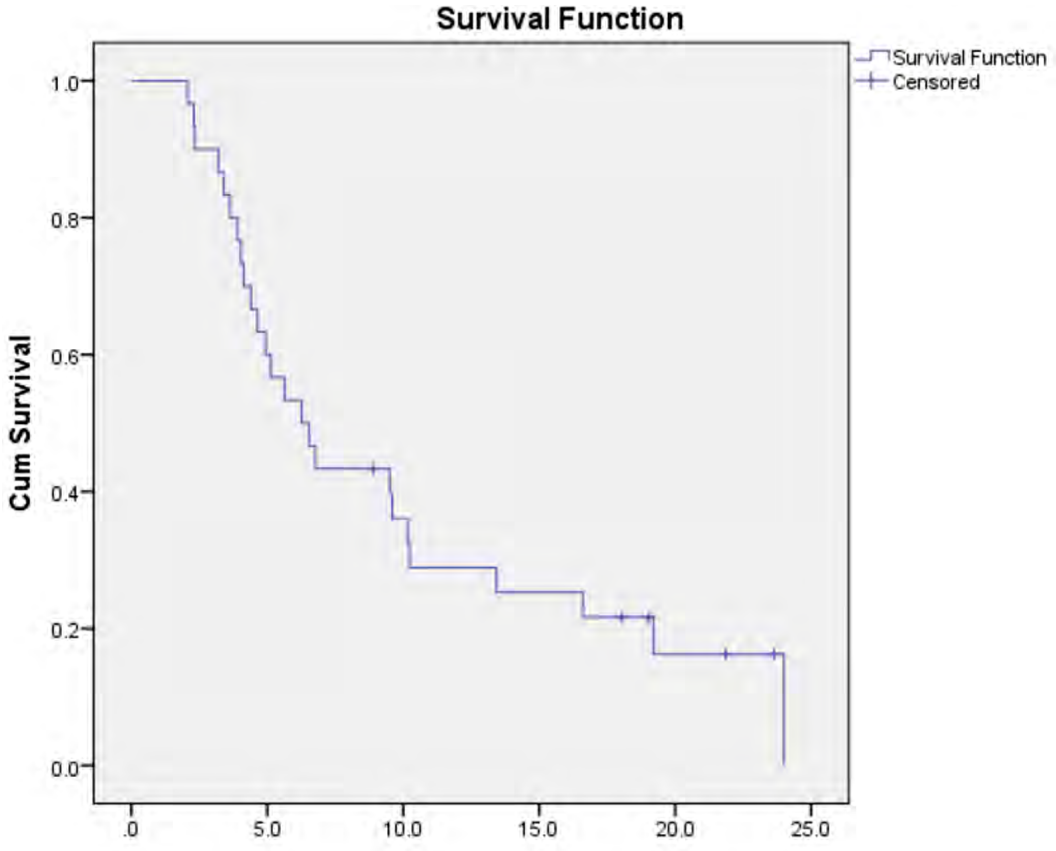
RESULTS

The mean PTV volume was 271±137.3 cc. The dosimetric analysis for both target volume and critical structures is reported in Table 3. Conformity and homogeneity indices (0.98±0.02 and 0.08±0.03) were proper, considering that the ideal values are 1 and 0. The mean monitor units for one fraction delivery were 517±112.7.

TABLE 3. *Planning Target Volume (PTV) and Organs at Risk (OARs) dosimetry*

Structure	Value±SD
PTV	
$D_{2\%}$ (Gy)	61.74 ± 0.32
$V_{95\%}$ (%)	97.65 ± 2.01
CI	0.98 ± 0.02
HI	0.08 ± 0.03
OARs	
Brainstem D_{max} (Gy)	62.31 ± 1.01
Spinal Cord D_{max} (Gy)	5.83 ± 7.34
Ipsilateral Eye D_{max} (Gy)	23.25 ± 15.85
Contralateral Eye D_{max} (Gy)	10.88 ± 5.81
Ipsilateral optic nerve D_{max} (Gy)	28.38 ± 20.47
Contralateral optic nerve D_{max} (Gy)	17.19 ± 10.85
Ipsilateral Lens D_{max} (Gy)	5.52 ± 1.82
Contralateral Lens D_{max} (Gy)	4.58 ± 2.02
Optic Chiasm D_{max} (Gy)	36.53 ± 17.76
Pituitary Gland D_{max} (Gy)	32.45 ± 18.7
Normal Brain D_{max} (Gy)	62.31 ± 1.01
Normal Brain V_{18Gy} (%)	51.11 ± 17.11

At a median follow-up of 12 months, we report a median PFS of 6.3 months (95%CI: 4.1-8.5) and a median OS of 15 months (95%CI: 7.9-22.2) (Figure 2).



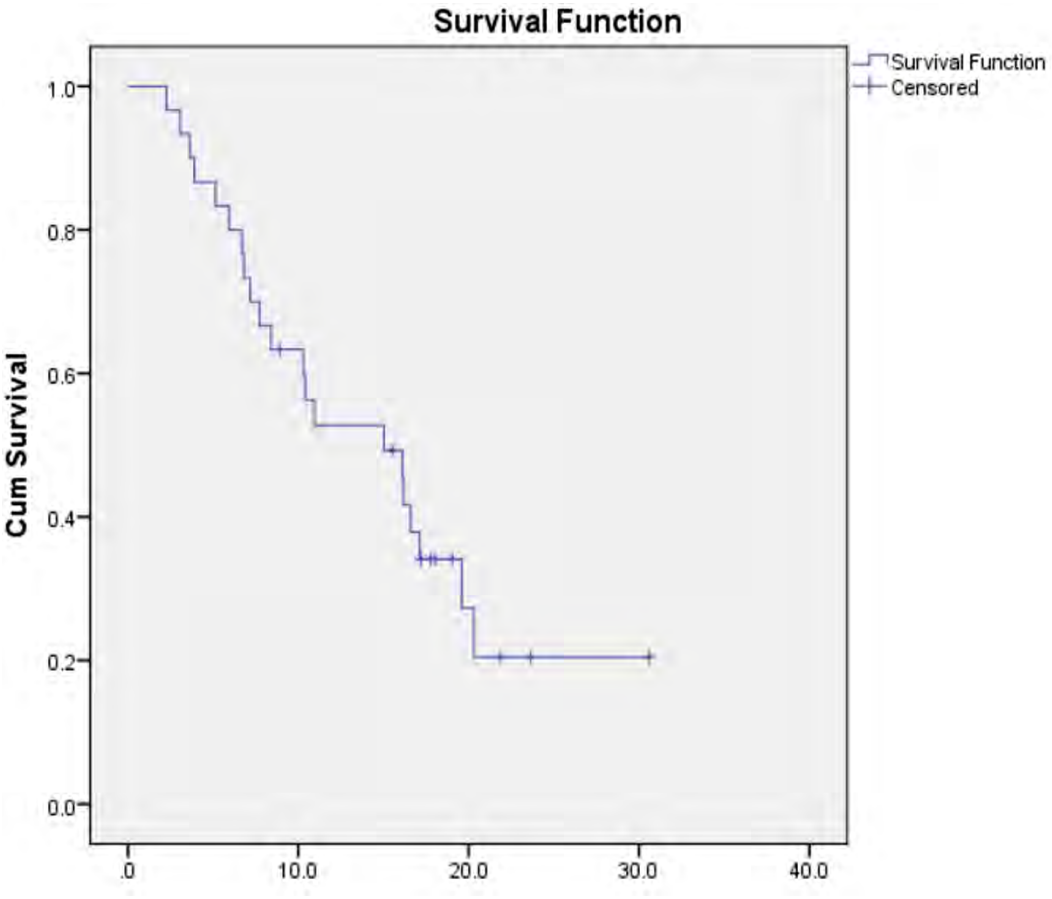


FIGURE 2. *Progression free survival (PFS) – left and overall survival (OS) – right*

During concomitant chemoradiotherapy, all patients were evaluated for toxicity. Important haematological toxicity occurred in 3 cases (grade III thrombocytopenia in 2 patients and grade III anaemia in 1 patient). Four patients developed grade II fatigue and 3 patients needed medical therapy for deep venous thrombosis.

Twenty-five (83.3%) patients have relapsed. Recurrence at the treatment site occurred in the majority of cases (22 patients), while 3 cases associated out of field progression. Salvage treatment consisted of surgery in 2 cases, reirradiation in 1 case and second-line chemotherapy in 9 cases.

DISCUSSION

VMAT has been described as a novel extension of IMRT and it is able to achieve the necessary modulation during a gantry rotation by varying continuously the instantaneous dose rate, multileaf collimator apertures and speed of rotation (15). Since its availability, this technique has been explored in various tumor sites, but studies have focused more on planning and dosimetry and fewer publications with survival analysis emerged (16). Therefore, we wanted to report both dosimetric and clinical outcome of GBM patients from our institution since VMAT implementation.

Several reports reviewed the impact of VMAT on high-grade gliomas (HHG) dosimetry. Shaffer et al. (7) described in 10 frontal and temporal HHG, that overlapped the brainstem and/or chiasm and or/optic nerve, similar normal brain maximum dose 63.1 Gy (62.4-63.9), higher values, for optic structures (D_{max} for optic chiasm 52.5 Gy, D_{max} for ipsilateral optic nerve 51.3 Gy and D_{max} for contralateral optic nerve 35.2 Gy) and fewer MU (363), when compared to our research. In another study involving 10 GBM patients, the dosimetric results with triple arc VMAT are slightly better regarding HI and CI (0.06±0.01 and 1±0.02), but similar to our values among maximum absorbed doses for OARs (17).

VMAT utilization for every patient may be difficult, as it requires longer treatment time preparation and more human resources, therefore researchers tried to develop selection criteria for HHG patients benefiting more from VMAT optimization. Tanabe *et al.* (18) considered that VMAT is more appropriate for GTVs larger than 130.5 cm^3. With a "cone down" contouring technique, PTV scored a median $V_{95\%}$ of 95.7% (76.7-99.3), a median $D_{2\%}$ of 63 Gy (62-63.8), a median HI of 0.11 (0.085-0.24) and a median CI of 0.93 (0.69-0.96). Median $D_{2\%}$ for normal brain recorded 61.3 Gy (59.2-62.1).

In a large cohort of 174 patients that underwent VMAT, Navarria et al. (5) reported dosimetric PTV values of 97.2±21.8% for $V_{95\%}$, 0.09±.0.04 for HI and 1.04±0.02 for CI, while survival data associated a median PFS of 1.29±0.13 years and median OS of 1.56±0.09 years.

Our survival analysis describes a median PFS and OS of 6.3 months (95%CI: 4.1-8.5) and 15 months (95%CI: 7.9-22.2). These results are similar with the ones reported by Stupp et al. (2) in the radiotherapy plus concomitant temozolomide of the multicentric phase III trial that recorded a median PFS of 6.9 months (95% CI: 5.8-8.2) and OS of 14.6 months (95% CI: 13.2-16.8).

CONCLUSION

Regardless of the new advances in imaging and radiotherapy, the prognosis of GBM patients remains dismal and our results do not exceed survival expectation. However, we document dosimetric parameters with VMAT technique in our practice comparable to results from international cancer centers.

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