

research article

Impact on radiation dose and volume V57 Gy of the brain on recurrence and survival of patients with glioblastoma multiformae

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Background. The aim of the study was to analyze impact of irradiated brain volume V57 Gy (volume receiving 57 Gy and more) on time to progression and survival of patients with glioblastoma.

Patients and methods. Dosimetric analysis of treatment plan data has been performed on 70 patients with glioblastoma, treated with postoperative radiochemotherapy with temozolomide, followed by adjuvant temozolomide. Patients were treated with 2 different methods of definition of treatment volumes and prescription of radiation dose. First group of patients has been treated with one treatment volume receiving 60 Gy in 2 Gy daily fraction (31 patients) and second group of the patients has been treated with "cone-down" technique, which consisted of two phases of treatment: the first phase of 46 Gy in 2 Gy fraction followed by "cone-down" boost of 14 Gy in 2 Gy fraction (39 patients). Quantification of V57 Gy and ratio brain volume/V57Gy has been done. Average values of both parameters have been taken as a threshold value and patients have been split into 2 groups for each parameter (values smaller/larger than threshold value).

Results. Mean value for V57 Gy was 593.39 cm³ (range 166.94 to 968.60 cm³), mean value of brain volume has been 1332.86 cm³ (range 1047.00 to 1671.90 cm³) and mean value of brain-to-V57Gy ratio was 2.46 (range 1.42 to 7.67). There was no significant difference between two groups for both V57 Gy and ratio between brain volume and V57 Gy.

Conclusions. Irradiated volume with dose 57 Gy or more (V57 Gy) and ration between whole brain volume and 57 Gy had no impact on time to progression and survival of patients with glioblastoma.

Key words: irradiation V57; glioblastoma

Introduction

Glioblastoma is most common and most aggressive brain tumor with incidence of 2-3 per 100 000 population according to GLOBOCAN.¹ Incidence of glioblastoma accounts 12-15% of all intracranial tumors and approximately 50-60 of all astrocytic tumors.^{2,3} Diagnosis, treatment and follow up of patients with glioblastoma and multidisciplinary approach and best results are achieved in specialized centers, which can offer all treatment modalities when it is needed and which are more

experienced with larger volume of cases.⁴ Mutual understanding and collaboration of team of professionals is of paramount importance for obtaining best medical care and best clinical results (tumor control and survival). During last two decades, major advantages have been made in enhancing precision of radiation treatment and shaping of radiation dose to increase dose distribution in target and to decrease radiation dose in organs at risk. Three-dimensional conformal radiotherapy and its derivatives, Intensity Modulated Radiation Therapy (IMRT) and Volumetric Arc Therapy (VMAT) are

now standard of treatment for patients with glioblastoma.⁵⁻⁷ Standard postoperative treatment of patients with glioblastoma consist of postoperative radiotherapy with temozolomide followed by adjuvant temozolomide.⁸⁻¹¹ Radiotherapy is corner-stone of multimodality approach and it is considered as treatment with highest benefit of all three treatment modalities. Despite the major advantages in personalization and precision of the radiotherapy treatment, median survival of patients with glioblastoma is still between 12 and 16 months from diagnosis.⁴

In general there are two major approaches in definition of gross tumor volume (GTV) in patients with glioblastoma. In studies conducted by EORTC (European Organization for Research and Treatment of Cancer) only one contoured gross tumor volume is used which is defined as an enhanced visible tumor on MR images prior the surgery expanded respectively to clinical target volume (CTV) and planning target volume (PTV) according ESTRO-ACROP Guidelines.⁷

In contrast in studies conducted by RTOG (Radiation Therapy Oncology Group) definition of volumes in according to “cone-down” approach, which means that there are virtually two volumes defined on preoperative and/or postoperative MR, one initial (larger) volume and second “cone-down” volume or boost volume (smaller). With “cone-down” approach in some clinical situation it is possible do decrease radiation dose to the brain which could have impact on survivorship of patients with glioblastoma.^{12,13}

Volume of the tumor measured as initial tumor size or preoperative tumor size and residual disease is generally considered as a prognostic factor for survival and recurrence in patients with glioblastoma.^{14,15} There are various approaches and quantification of what is really visible tumor and

consequently, what volume should be irradiated in order to minimize tumor recurrence, but reaching consensus between different research groups is still under debate. Definition of volume of the tumor, depends of imaging modality used, resolution of imaging modality, processing algorithms and various other variables.¹⁵⁻¹⁸

After definition of gross tumor volume there is still debate, what is most appropriate clinical treatment volume (CTV). There are different approaches, which are evolving together with advances of imaging. CTV as concept in glioblastoma is difficult to define and different research groups have various definitions and no-one of these definitions is absolutely true or false.²⁰⁻²⁸

There are more or less well defined criteria for definition of CTV and PTV for patients with glioblastoma specially treated in clinical trial setting, as AVAGlio and Centric trials, recently.^{28,29}

Also it is well known fact that in daily clinical practice clinicians are adopting volume delineation according to their clinical setting and capabilities, and using delineation according to RTOG, EORTC or institutional standards.³⁰

In our study we treated patients with two different approaches on delineation on treatment volumes using one phase treatment EORTC “like” and RTOG “like” approach, but randomization was used for assignment of patients in the group as a part of the standard protocol for treatment developed in the institution.

Patients and methods

This study was approved by the ethical committee of Medical Faculty at University “Ss. Cyril and Methodius” in Skopje and University Clinic of Radiotherapy and Oncology in Skopje (Number: 03-2455/2) and was carried out according to the Declaration of Helsinki.

Total of 70 patients, with glioblastoma multiforme has been included in this study. Patient accrual has been performed in the period from January 2013 to December 2015. All patients have been previously surgically treated with maximal safe resection of the primary tumor and definitive histological diagnosis has been established as a glioblastoma multiforme according to the last World Health Organization classification.³

After referral to radiotherapy treatment, patients have been scheduled for computed tomography (CT) simulation in treatment position. CT scan has encompassed cranial region according to

TABLE 1. Patient characteristics

	Group 1 (1 v) 31 patients	Group 2 (cone-down) 39 patients
Age	Range 29–71, median age 56	Range 27–75, median age 56
Sex	Male - 14 Female - 17	Male - 21 Female - 18
Location of the primary lesion	5 - frontal lobe 6 - temporal lobe 11 - parietal lobe 2 - occipital lobe 7 - overlapping	8 - frontal lobe 15 - temporal lobe 9 - parietal lobe 1 - occipital lobe 6 - overlapping
Average time from surgery to RT (days)	36 (25–55)	39 (24–74)
V57 Gy	< 600 cm ³ - 15 > 600 cm ³ - 16	< 600 cm ³ - 23 > 600 cm ³ - 16

institutional protocol with slice thickness of 2 mm. For immobilization purpose thermoplastics masks and head rests have been used during simulation and treatment.

After computed tomography simulation, image fusion with preoperative and/or postoperative MR scan has been done using automatic MR-CT fusion using non deformable algorithm with manual correction, only if necessary, leaded by decision of radiation oncologist. MR-CT fusion has been done using transversal MR images using T1 with contrast and T2/FLAIR sequence. In the analysis has been included only patents who finished complete treatment, total of 70 patients from included 78 patients. Eight patients did not finish treatment, and were excluded from analysis.

Patients have been randomly assigned to one of the groups on the basis of referral to the department. Patients with odd hospital number have been assigned to the first group, and patients with even hospital number have been assigned to second group. In the first group of the patients (total of 31 patients), delineation was based on T2/FLAIR and T1 with contrast enhancements and only one GTV volume has been contoured. After delineation of GTV, CTV was expanded for 2 cm, taking in account anatomic boundaries and omitting, if possible, organs at risk. CTV was expanded to PTV with addition of margin of 5 mm, which is considered institutional standard. In the second group (total of 39 patients), "cone-down" approach has been used and delineation of target volume has been done in two phases and two GTV volumes have been delineated. First or initial volume GTV46, has been delineated based on MR images using T2/FLAIR abnormalities. Expansion of GTV to CTV has been done with margin of 2 cm, taking in account anatomic boundaries and avoidance of organs at risk, similar as in first group. Further expansion of CTV to PTV was with margin of 5 mm. Cone down volume or boost volume has been delineated on contrasts enhanced T1 MR Image set. CTV has been expanded for 2 cm, and PTV expanded further for 0.5 cm, as initial delineated volume.

Dose prescription for patients in the first group was 60 Gy in 30 daily fractions of 2 Gy and in second group, prescribed dose for initial volume was 46 Gy in 23 fractions and for the "cone-down" volume additional 14 Gy in 7 fractions. Initial and "cone-down" volumes have been treated with 2 Gy daily fractions. Treatment schedules for both groups were 5 fractions on each consecutive day in 7 days week.

Treatment planning has been done using Varian Eclipse planning system version 10.0.45.0 and the most appropriate treatment plan have been selected in order to achieve dose distribution in target(s) and in organs at risk in order to fulfill QUANTEC criteria.³¹⁻³³

Together with radiotherapy all patients were treated according to "Stupp protocol" and received concurrent chemotherapy with temozolomide, followed by adjuvant temozolomide.³⁵

After treatment, patients undergo follow up which consisted of physical examination every month which corresponded with adjuvant chemotherapy cycle, MR every 3-4 months and other clinical examination if necessary. Follow up strategy was in line with ESMO clinical recommendations and modified according to specific clinical situation.⁹

Two volumetric parameters were selected as relevant in order to predict exposure to brain as an organ at risk in our series of patients. First parameter is volume which received 57 Gy and more in cm^3 , "V57Gy", and second parameter is calculated as a ratio between brain volume and "V57Gy", calculated as numeric coefficient, decimal number.

"V57Gy" was calculated using TPS software and using build in algorithms for converting isodose level to structure. This function is standard in majority of modern treatment planning systems available in the market and it is available as a standard option in our institutional TPS.

Patients has been separated in 2 groups for both parameters and threshold values were estimated for "V57Gy" equal to 600 cm^3 and for ratio between brain volume and "V57Gy" equal to 2.4 presented as a decimal number.

Based on the first parameter, patents were split on 2 groups. The first group of patients with "V57Gy" up to 600 cm^3 consisted of 38 patients, and second group of patients with "V57Gy" more than 600 cm^3 consisted of 32 patients.

According to second parameter, ratio between brain volume and "V57Gy", patients were also split into 2 groups: patients with ratio less than 2.4 numeric value (40 patients) and patients with ratio of more than 2.4 (30 patients).

Results

Median follow up of all 70 patients was 12 months (range from 4 to 33 months). Median time to progression (recurrence) was 12 months and median

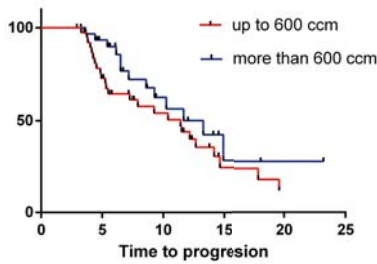


FIGURE 1. Time to progression for "V57Gy" volume. Threshold value was 600 cm³.

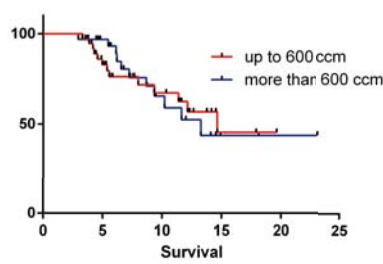


FIGURE 2. Overall survival for "V57Gy" volume. Threshold value was 600 cm³.

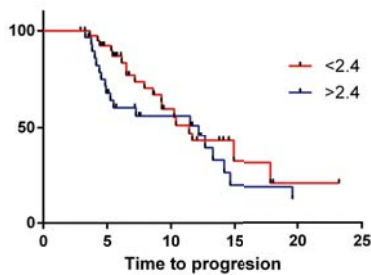


FIGURE 3. Time to progression for ratio between brain volume and "V57Gy" volume. Threshold value was 2.4.

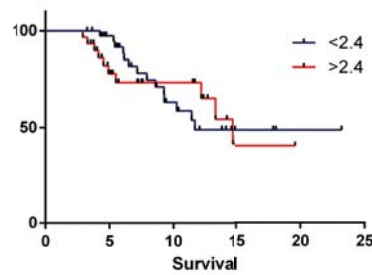


FIGURE 4. Overall survival for ratio between brain volume and "V57Gy" volume. Threshold value was 2.4.

survival was calculated as 24 months using Kaplan Meir method.³⁵

Survival analysis using Kaplan Meir method has been done on two parameters for both time to progression (recurrence) and overall survival. Comparison of survival has been calculated using Matel-Cox and Gehan-Breslow-Wilcoxon (log-rank) tests.^{36,37}

For volumetric parameter of "V57Gy", comparison of patients with "V57 Gy" of less than 600 cm³ (38 patients) and more than 600 cm³ (32 patients) has been done. Time to progression for group of patients with "V57Gy" ≤ 600 cm³ was 11.43 months and for group of patients with "V57Gy" > 600 cm³ was 13.29 and for overall survival, 14.64 and 13.29 months. (Figure 1, 2). There was not any significant difference for both time to progression ($p = 0.2065$) and overall survival ($p = 0.9970$).

For second parameter, calculated as numeric value, ration between whole brain volume and "V57Gy" volume, comparison for time to progression and overall survival for patients with numerical value ≤ 2.4 (40 patients) and numeric value > 2.4 (30 patients) has been done. Median time to progression for group of patients with value ≤ 2.4 was 11.43 months and for group of patients with numeric value > 2.4 was 12.18 months. Overall survival

was 11.68 and 14.64 months respectively. There was no significant difference in time to progression ($p = 0.2881$) and overall survival ($p = 0.8572$) between this two groups (Figure 3, 4).

Discussion

Based on this data we concluded that these volumetric parameters did not have any impact on time to progression and overall survival on patients with glioblastoma, treated with postoperative radiochemotherapy. In general, in malignant tumors, size of the tumor is considered as an independent prognostic factor which is described as a T stage according to UICC Classification³⁸, but due to specific characteristics of brain tumors, TNM classification for prognostic values is not applicable, but rather WHO classification which do not correspond to size of the tumor. According to EORTC and NCIC nomogram for predicting outcome in patients with newly diagnosed glioblastoma, there are several factors which are predicting survival. Following parameters are suggested as potential prognostic factors, which should be reported in all clinical studies: MGMT promoter methylation status, age, performance status, extent of resection, and Mini Mental State Examination (MMSE).³⁹

Volumetric parameters calculated in our study did not have impact on local control and overall survival. In our study threshold value was estimated as an average value from our series of the patients. In the future studies we are planning to include more patients for evaluation of volumetric parameters and to create more strict constraints with higher gradient. In this case we had approximation that there will be difference in both recurrence and survival for patients with smaller irradiated volumes compared with very large irradiated volume, which should be proven in future studies.

Radiation treatment of CNS tumors has been evolved in the past two decades with introduction of more precise imaging and treatment devices in radiation oncology followed by development of more precise treatment techniques. Despite the fact that modern treatment devices are able to deliver higher dose to specified tumor volume, using possibility to conform beams in order to protect critical organs there, are not positive studies to prove that escalation of radiation dose beyond 60 Gy with standard fractionation will have impact of the disease control.⁴⁰ There are some exceptions regarding dose and fractionation for patients with poor performance status. Recent studies showed that

shortening duration of radiotherapy treatment with increasing daily fraction (40 Gy in 15 fractions or 25 Gy in 5 fractions) is with equivalent results regarding survival and quality of life.⁴² In our study we showed that decreasing of treated volume with cone-down approach did not have any impact on marginal recurrence in glioblastoma patients treated with radiotherapy and concurrent and adjuvant temozolomide. These results are in line with recent published studies that reducing treated volume with careful delineation of visible tumor on MR, will not have any impact on marginal recurrence.⁴²⁻⁴⁵

Finally, careful selection of imaging modalities, registration and selection of the most suitable treatment plan is of paramount importance for obtaining best results and obtaining best local control during radiation treatment of patients with glioblastoma.

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