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Changing Trends in Radiotherapy for Glioblastoma Multiforme and Effects on Normal Tissue Doses

Glioblastoma Multiforme Radyoterapisinde Değişen Eğilimler ve Normal Doku Dozlarına Etkileri

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Abstract/Öz

Introduction: The aim of the study is to reveal the changing trends in radiotherapy (RT) for glioblastoma multiforme (GBM) to date and to show the changes in the organs at risk (OARs) doses.

Methods: We replanned 10 patients with GBM who were previously irradiated. Rigid fusion was performed through pre- and postoperative magnetic resonance imaging (MRI) and simulation computed tomography, and nine separate volumes were created. The volumes varied from whole brain RT (WBRT) to postoperative two-phase irradiation, whereas RT application ranged from two dimensional Co-60 treatment to three-dimensional (3D) volumetric modulated arc therapy (VMAT). OARs were contoured and doses were noted. A 3D-conformal RT (3D-CRT) plan of the volume created by preoperative MRI was compared to 3D-CRT and VMAT plans generated by postoperative MRI.

Results: During WBRT, the normal brain tissue received 45-60 Gy. The median brain planning target volume (PTV) Dmean decreased to 35 Gy through VMAT. According to both PTV-RTOGpreop and PTV RTOGpostop 3D-CRT planning, there was no difference in all OARs doses between plans, including the brain-PTV initial volume Dmean and brain-PTV boost Dmean doses. Significantly lower OARs doses were obtained from 3D-CRT plans based on both PTV-RTOGpreop and PTV-RTOGpostop volumes with the VMAT planning.

Conclusion: With changing trends in RT for GBM, there has been a significant decrease in treatment volumes and normal tissue doses. According to the postoperative volume definition of the Radiation Therapy Oncology Group, lower normal tissue doses are obtained from VMAT plans compared to the conformal treatment plans.

Keywords: Intensity modulated radiotherapy, glioblastoma multiforme, volumetric modulated arc therapy, 3D conformal radiotherapy

Amaç: Çalışmanın amacı glioblastoma multiforme (GBM) radyoterapisindeki (RT) geçmişten günümüze değişen eğilimlerin ortaya konulması ve risk altındaki organ dozlarındaki değişimin gösterilmesidir.

Yöntemler: GBM tanısı ile postopereatif temozolamid ve radyoterapi ile tedavi edilen 10 hastanın simülasyon bilgisayarlı tomografi (simBT) görüntüleri retrospektif olarak incelenerek pre- ve postoperatif manyetik rezonans görüntüleri (MRI) ile rjiid füzyon yapıldı ve 9 ayrı volüm oluşturuldu. Volümler total kranyum ışınlamadan postoperatif iki fazlı ışınlamaya değişkenlik gösterirken, RT uygulaması 2-boyutlu (2B) Co-60 tedavisinden 3-boyutlu (3B) volumetrik ark tedaviye (VMAT) değişiyordu. Risk altındaki organlar (organs at risk - OAR) konturlandı. Beyin-PTV Dmean, beyin sapı Dmax, göz Dmax ipsilateral/kontralateral, kiazma Dmax, koklea Dmean ipsilateal/kontralateral, lakrimal gland Dmax ipsilateral/konrtalateral, lens Dmax ipsilateral/kontralateral, pituiter gland Dmax dozları kaydedildi. 7, 8, 9. planlar (preop MRI'dan oluşturulan volümün 3B-konformal radyoterapi-3B-KRT planı ile postop MRI'dan oluşturulan 3B-KRT ve VMAT planları) karşılaştırıldı. Paired sample t testi ile istatistiksel analiz yapıldı.

Bulgular: Total kranyum RT uygulandığı dönemlerde normal beyin dokusunun hepsi 45-60 Gy alırken VMAT ile beyin-PTV Dmean medyan 35 Gy'e düşmüştür. Aynı zamanda göz ve lensler dışında risk altındaki organlar verilen tüm dozu alarak 60 Gy uygulanan gruplarda doz sınırlamaları aşılmıştır. Hem PTV-RTOGpreop hem de PTV-RTOGpostop 3D-CRT planına göre beyin-PTVinitial volüm Dmean ve beyin-PTVboost Dmean dozları dahil olmak üzere tüm OAR dozlarında iki plan arasında istatistiksel anlamlı fark yoktu. VMAT planı ile hem PTV-RTOGpreop hem de PTV RTOGpostop volümlerine göre yapılan 3D-CRT planlarından istatistiksel anlamlı daha düşük OAR dozları elde edildi.

Sonuç: Tarihsel süreçte ışınlanan volüm ve normal doku dozlarında belirgin azalma olmuştur. RTOG'nin postoperatif volüm tanımına göre konformal ve VMAT planları karşılaştırıldığında VMAT planlamada daha düşük normal doku dozları elde edilmektedir.

Anahtar Kelimeler: Yoğunluk ayarlı radyoterapi, glioblastoma multiforme, volümetrik ark tedavisi, üç boyutlu konformal radyoterapi

Introduction

Glioblastoma multiforme (GBM) is the most fatal and frequent primary brain malignancy in adults (1). Addition of temozolomide to adjuvant radiotherapy (RT) has improved the survival rate (2). The standard treatment for GBM includes surgery, RT, and chemotherapy (3-5). RT has been routinely used in the treatment of brain tumors since the 1940s (6). Although the use of three-dimensional conformal radiation therapy (3D-CRT) is regarded as the standard treatment (7, 8), intensity modulated radiation therapy (IMRT) is accepted as an alternative of 3D-CRT; moreover, it can minimize treatment-associated side effects (9). The use of proton RT is also increasing (10). RT for GBM was initially started as whole brain irradiation. The techniques in RT have been improved by developing different doses and applications and by determining the organs at risk (OARs) and dose limits. The aim of the present study is to reveal the changing trends in RT for GBM to date and to show the changes in OARs doses.

Methods

Simulation computerized tomography (simCT) and cranial magnetic resonance imaging (MRI) scans of 10 patients who were treated with adjuvant temozolomide after surgical resection following concomitant temozolomide and RT were selected from the archives of the Institute of Oncology of İstanbul University. Following this selection, the previous basic scans of the patients were recalled into the RT simulation station. In fact, no patient joined the simulation process. Patient data were

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Table 1. Comparison of normal tissue doses generated from three different radiotherapy plans according to RTOG volumes

	A Mean (SD) median (min-max)	B Mean (SD) median (min-max)	C Mean (SD) median (min-max)	A-B p	A-C p	B-C p
Brain-PTV phase I D_{mean}	39.6 (12) 41.7 (18.1-52.4)	40.2 (8.4) 43.5 (22.6-48.7)	24.3 (3.3) 24.1 (16.9-28.5)	0.693	0.001	<0.001
Brain-PTV boost D_{mean}	41.4 (12.2) 44 (19.3-53.4)	42.9 (7.6) 45.5 (25.8-51.4)	33.6 (5.6) 34.4 (19.8-39.1)	0.458	0.021	<0.001
Optic chiasma D_{max}	55.5 (18.9) 62.1 (2.2-63.6)	54.8 (18.5) 62 (3.4-63.2)	48.6 (11) 52.9 (18.5-54.3)	0.463	0.030	0.029
Contralateral cochlea D_{mean}	42.2 (28.1) 59 (0.7-60.9)	38.4 (22.2) 48.3 (1.7-56.8)	12 (6.9) 13.8 (2.3-20.2)	0.183	0.002	0.001
Ipsilateral cochlea D_{mean}	43.6 (29.3) 61 (0.6-63)	42.7(25.3) 57.2 (1.5-60.8)	22.9 (11.5) 28.5 (2.8-33.5)	0.624	0.006	0.002
Brainstem D_{max}	55.8 (11.9) 61.6 (28-62.1)	59 (4.4) 60.4 (47-61.4)	53.6 (4.3) 55.3 (43.2-58.4)	0.349	0.484	<0.001
Pituitary gland D_{max}	48.1 (24.4) 62.1 (1.8-63.1)	53.5 (18.6) 61.4 (2.4-62.6)	41.9 (12.6) 46.7 (15.1-51.8)	0.289	0.151	0.005
Contralateral eye D_{max}	35 (21.3) 36.2 (0.1-58.4)	37.9 (21) 40.1 (0.2-60)	23.4 (9) 23.2 (7.9-38.2)	0.097	0.022	0.007
Ipsilateral eye D_{max}	38.3 (23.5) 41.3 (0.1-62.6)	42 (22.8) 46.5 (0.2-62.3)	34.5 (13.2) 35.7 (8.5-49.4)	0.100	0.333	0.053
Contralateral lacrimal gland D_{max}	30.3(21) 34.3 (0.2-58.2)	32.4(20.5) 36.4 (0.2-60)	21.9(8) 22.1 (10.1-35.5)	0.166	0.079	0.032
Ipsilateral lacrimal gland D_{max}	35.7 (23.6) 40.6 (0.1-61.4)	39.9 (22.9) 47.6 (0.2-62.2)	32.3(10.6) 36.5 (9.8-44)	0.063	0.475	0.095
Contralateral lens D_{max}	5.9 (4.2) 5.4 (0.06-12.7)	6.2 (4.2) 6 (0.1-15.3)	7.7(2) 7.7 (4.2-11.9)	0.619	0.084	0.183
Ipsilateral lens D_{max}	5.1(3.8) 3.9 (0.05-12)	5.5(4.4) 3.9 (0.1-15.5)	7.9(2.3) 7.9 (4.4-12.5)	0.415	0.005	0.066

A. $RTOG_{preop}$: two-phase conformal radiotherapy plan using preoperative volumes according to RTOG 9710; B. $RTOG_{postop}$: two-phase conformal radiotherapy plan using postoperative volumes according to actual RTOG recommendations; C. $RTOG_{postop}$: two-phase volumetric modulated radiation therapy plan using postoperative volumes according to actual RTOG recommendations; X: mean value; SD: standard deviation; PTV: planning target volume

de-identified. Because of the retrospective and simulative nature of our study, no informed consent and no ethical approval were obtained. However, the study was performed in accordance with the Declaration of Helsinki. A rigid fusion was performed through the MIM software (Version 6.5, MIM Software Inc.) using simCT and pre- and postoperative MRI contrast-enhanced T1 and T2/flair sequences images. OARs and dose constraints were determined according to the European Organisation for Research and Treatment of Cancer-Advisory Committee on Radiation Oncology Practise (EORTC-ACROP) guidelines and a study by Scoccianti et al. (11, 12). The optic chiasma, bilateral eyes, bilateral lenses, brainstem, bilateral cochlea, bilateral lacrimal glands, and pituitary gland were determined as the OARs. The brain planning target volume (PTV) was generated through PTV excluded from the brain tissue. In two-dimensional (2D) planning, the fields were manually created using multileaf collimators. Two-phase target volumes yielded from preoperative MRI images were determined in accordance with the Radiation Therapy Oncology Group (RTOG) 9710 protocol.

The $RTOG_{preop}$ phase 1 volume contained the volume of contrasted tumor with peripheral edema on preoperative MRI scan along with a 2-cm margin. The $RTOG_{preop}$ boost volume covered the contrasted lesion (without edema) on the preoperative MRI scan along with a 2.5-cm margin. The $RTOG_{postop}$ phase 1 volume included the volume of the postoperative cavity±residual tumor in contrast enhanced T1-weighted MRI scans and edema in the postoperative T2-weighted MRI scans along with a 2-cm margin. The $RTOG_{postop}$ boost volume included the resection cavity±residual tumor in contrast enhanced T1-weighted

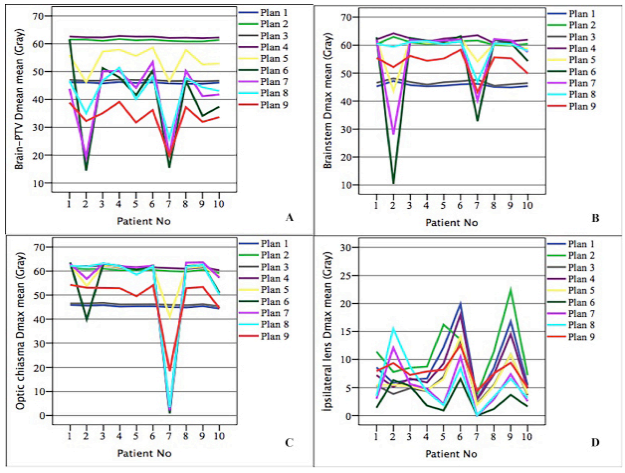

Figure 1. The doses of four organs at risk generated from 9 different plans
Plan 1: Whole brain radiotherapy (WBRT), 2D planning, Co-60, total dose 45 Gy in 25 fractions (fr); Plan 2: WBRT, 2D planning, Co-60 energy, total dose 60 Gy in 30 fr; Plan 3: WBRT, 2D planning, 6 MV energy, total dose 45 Gy in 25 fr; Plan 4: WBRT, 2D planning, 6 MV energy, total dose 60 Gy in 30 fr; Plan 5: WBRT in phase 1 and tumor bed boost in phase 2, 2D planning, 6 MV energy, phase 1 dose 40 Gy in 20 fr plus boost dose 20 Gy in 10 fr; Plan 6: PTV-RTOG$_{preop}$, 2D planning, 6 MV energy, phase 1 dose 46 Gy in 23 fr plus boost dose 14 Gy in 7 fr; Plan 7: PTV-RTOG$_{preop}$, 3D planning, 6 MV energy, 3D-CRT, phase 1 dose 46 Gy in 23 fr plus boost dose 14 Gy in 7 fr; Plan 8: PTV-RTOG$_{postop}$, 3D planning, 6 MV energy, 3D-CRT, phase 1 dose 46 Gy in 23 fr plus boost dose 14 Gy in 7 fr; and Plan 9: PTV-RTOG$_{postop}$, 3D planning, 6 MV energy, VMAT, phase 1 dose 46 Gy in 23 fr plus boost dose 14 Gy in 7 fr.

MRI scans along with a 2-cm margin. The 2D treatment planning was used to create plans 1-6, whereas the 3D planning was used to create plans 7-9. Plans 7 and 8 were performed through 3D-CRT, whereas plan 9 was generated through VMAT. The XIO v4.60 treatment planning system was used for all plans except the VMAT plan. The Eclipse V8.9 treatment planning system (Varian Medical Systems, Palo Alto, CA, USA) was used for VMAT. Treatment plans were prepared using three full rotation VMAT fields with different collimator angles. VMAT doses were prescribed according to The International Commission on Radiation Units and Measurements 83.

Co-60 was used for generating plans 1 and 2, and 6 MV was used for the remaining plans.
Plan 1: Whole brain RT (WBRT), Co-60 energy, total dose 45 Gy in 25 fractions (fr);
Plan 2: WBRT, Co-60 energy, total dose 60 Gy in 30 fr;
Plan 3: WBRT, 6 MV energy, total dose 45 Gy in 25 fr;
Plan 4: WBRT, 6 MV energy, total dose 60 Gy in 30 fr;
Plan 5: WBRT in phase 1 followed by tumor bed boost in phase 2, 6 MV energy, phase 1 dose 40 Gy in 20 fr plus boost dose 20 Gy in 10 fr;
Plan 6: PTV-RTOG$_{preop}$ phase 1, 6 MV energy, phase 1 dose 46 Gy in 23 fr plus boost dose 14 Gy in 7 fr;
Plan 7: PTV-RTOG$_{preop}$ phase 1, 6 MV energy, 3D-CRT, phase 1 dose 46 Gy in 23 fr boost dose 14 Gy in 7 fr;
Plan 8: PTV-RTOG$_{postop}$ phase 1, 6 MV energy, 3D-CRT, phase 1 dose 46 Gy in 23 fr plus boost dose 14 Gy in 7 fr; and
Plan 9: PTV-RTOG$_{postop}$ phase 1, 6 MV energy, VMAT, 46 Gy in 23 fr plus boost 14 Gy in 7 fr. Brain-PTV D_{mean}, brainstem D_{max}, bilateral eye D_{max}, optic chiasma D_{max}, bilateral cochlea D_{mean}, bilateral lacrimal gland D_{max}, bilateral lens D_{max}, and pituitary gland D_{max} doses were recorded. Plans 7, 8, and 9 were compared.

Statistical Analysis

The Statistical Package for Social Sciences software was used for the statistical analysis version 20 (IBM SPSS Corp.; Armonk, NY, USA) using the paired sample t-test. A $p<0.05$ was considered statistically significant.

Results

Through VMAT, the median brain-PTV D^{mean} decreased to 35 Gy, whereas all normal brain tissues received 45-60 Gy. Simultaneously, the OARs, except for the eye and the lenses, received overdoses in groups given 60 Gy. In Figure 1, the changes in four parameters of 9 plans are presented. Because both PTV-RTOG$_{preop}$ and PTV-RTOG$_{postop}$ had large treatment volumes, 3D CRT planning was possible using two opposing coplanar fields. No statistically significant difference was observed between the two plans for all OARs doses, including brain-PTV phase 1 D_{mean} and brain-PTV boost D_{mean} doses. In addition, the optic chiasma D_{max}, bilateral cochlea D_{mean}, brainstem D_{max}, pituitary gland D_{max}, and bilateral eye D_{max} median dose values were over the dose constraints. The PTV-RTOG$_{preop}$ 3D-CRT, PTV-RTOG$_{postop}$ VMAT plans were compared; doses of brain-PTV phase 1 D_{mean} (median: 41.7 Gy vs. 24.1 Gy, p=0.001), brain-PTV boost D_{mean} (median: 44 Gy vs 34.4 Gy, P=.021), chiasma D_{max} (median: 62.1 Gy vs 52.9 Gy, p=0.030), contralateral cochlear D_{mean} (median: 59 Gy vs 13.8 Gy, p=0.002), ipsilateral cochlear D_{mean} (median: 61 Gy vs 28.5 Gy, p=0.006), and contralateral eye D_{max} (median: 36.2 Gy vs 23.2 Gy, P=.022) were statistically lower in the RTOG$_{postop}$ VMAT plan. The lens D_{max} doses were within dose constraints except for one value in both groups, although the RTOG$_{postop}$ VMAT dose was higher in the lens D_{max} dose (median: 3.9 Gy vs 7.9 Gy, p=0.005). The PTV-RTOG$_{postop}$ 3D-CRT plan was compared to PTV-RTOG$_{postop}$ VMAT; the doses of brain-PTV initial D_{mean} (median: 43.5 Gy vs 24.1 Gy, p<.001), brain-PTV boost D_{mean} (median: 45.5 Gy vs 34.4 Gy, p<0.001), optic chiasma D_{max} (median: 62 Gy vs 52.9 Gy, p=0.029), contralateral cochlea D_{mean} (median: 48.3 Gy vs 13.8 Gy, P=.029), ipsilateral cochlea D_{mean} (median: 57.2 Gy vs 28.5 Gy, p=0.002), brainstem D_{max} (median: 60.4 Gy vs 55.3 Gy, p<0.001), pituitary gland D_{max} (median: 61.4 Gy vs 46.7 Gy, p=0.005), contralateral eye D_{max} (median: 40.1 Gy vs 23.2 Gy, p=0.007), and contralateral lacrimal gland D_{max} (median 36.4 Gy vs 22.1 Gy, p=0.0232) were statistically lower in the RTOG$_{postop}$ VMAT plan. The 3D-CRT made in two phases according to PTV-RTOG$_{preop}$ and RTOG$_{postop}$ volumes and the OARs doses made in the two-phase VMAT plan according to the RTOG$_{postop}$ volume are given in Table 1.

Discussion

The routine use of RT in brain tumors began in the 1940s with kilovoltage X-rays (13, 14). In the 1960s, 45-60 Gy RT was applied to the entire brain with megavoltage X-rays or Co-60 teletherapy devices (15, 16). In the present study, it was found that all the OARs and whole brain tissue, except for lenses, received a median (standard deviation [SD]) dose of 45 (3) Gy when 45 Gy WBRT was delivered after 2D planning through Co-60 or linear accelerators. The lenses were the only normal tissue that could be anatomically protected using protection blocks because of their distance from the brain tissue. Walker et al. (13) have found in 1979 that 50-60 Gy doses were associated with increased survival when compared with doses ≤45 Gy. Previously, 50-60 Gy was applied to the whole brain. On performing 60 Gy 2D WBRT with Co-60 and linear accelerators in the present study, it was observed that all the OARs and whole

brain tissue, except for the lenses, received a median (SD) dose of 60 (3) Gy. All the OARs exceeded the dose constraints that need to be considered. In the 1970s, some centers were delivering an initial dose of 30-46 Gy as WBRT, followed by 20-30 Gy irradiation to the tumor bed; hence the two-phase treatment was used (17-21). Initially, CT (in the 1970s and 1980s) and then MRI (in the late 1980s) was used for delineating RT target volumes (22). Thereafter, two-phase treatment plans including phase 1 and boost volumes were used by abandoning WBRT. Previously, two-phase target volumes were created with the aid of preoperative imaging, predominantly considering preoperative tumor and edema volumes. In this study, we compared two different two-phase plans using 6 MV energy through WBRT (40 Gy/20 fr) plus boost (20 Gy/10 fr) and PTV-RTOGpreop phase 1 (46 Gy /23 fr) plus PTV-RTOG boost (14 Gy/7 fr) volumes generated according to RTOG 9710. Between these two plans, there were no significant differences in terms of brain-PTV initial D_{mean}, chiasma D_{max}, and brainstem D_{max} doses. However, in the plans generated according to RTOG 9710, the brain-PTV boost D_{mean}, contralateral cochlear D_{mean}, contralateral eye D_{max}, contralateral lacrimal gland D_{max}, ipsilateral lacrimal gland D_{max}, contralateral lens D_{max}, and ipsilateral lens D_{max} doses were significantly lower, thereby sparing normal OARs better. In addition to technological advances, approaches in generating irradiation volumes for GBM were changing in accordance with clinical evaluations. The side effects of RT in neurological tissues have led to this change. Brain irradiation is associated with neurotoxic side effects, including radionecrosis and cognitive impairment (23, 24). For the first time, Chang et al. (25) compared the RTOG volume, including peritumoral edema in preoperative MRI and target volumes in which peritumoral edema is not taken into consideration, but in which the residual tumor in the postoperative MRI +/- is targeted. According to both RTOG and MD Anderson Cancer Center plans, they revealed that 90% of the recurrences were central and within the area. Currently, guidelines recommend using a postoperative MRI for defining/delineation target volume for RT in GBM. Different cooperative groups have target volume delineation that include or exclude peritumoral edema (26). In the present study, we compared the 3D-CRT plan of preoperative volume based on RTOG, the 3D-CRT plan of postoperative volume based on RTOG, and the VMAT plan of postoperative volume based on RTOG. The doses of OARs obtained in the VMAT plan, made in two phases according to PTV-$RTOG_{preop}$ and PTV-$RTOG_{postop}$ volumes and made in two phases according to the $RTOG_{postop}$ volumes with 3D-CRT and brain-PTV initial/boost D_{mean}, were significantly lower. Although 3D-CRT is accepted as the standard in general use, IMRT and VMAT are increasingly used in tumors with large volume and near OARs (9-11). The 3D-CRT is often sufficient in cases of spherical frontal or parietal tumors, whereas more successful plans can be made with IMRT or VMAT in irregularly shaped, brainstem or near-orbit-like tumors (27, 28). VMAT is usually preferred because it will provide a faster treatment plan and treatment application with conformity similar to IMRT. Currently, the dose to be preferred in a young patient, who is fit and whose performance score is good, is 60 Gy in 30 fr with concomitant temozolomide (11). Hypofractionated schedules are suitable for elderly or patients with a poor performance status (such as 40 Gy in 15 fr or 34 Gy in 10 fractions) (29,30).

Conclusion

RT for disease control of GBM is important. With changing trends, there has been a significant decrease in the treatment volumes and normal tissue doses. Currently, the volume is generated according to the postoperative cranial MRI in the target volume delineation. When conformal and VMAT plans are compared according to the postoperative definition of RTOG, lower normal tissue doses are obtained in VMAT plans. The 3D-CRT can be used depending on tumor location, whereas VMAT is advantageous when the treatment volume is close to OARs.

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Informed Consent: Informed consent was not taken from patients due to the retrospective nature of the study.

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Hasta Onamı: Çalışmanın retrospektif tasarımından dolayı hasta onamı alınamamıştır.

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