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

Glioblastoma Multiforme Radyoterapisinde Değişen Eğilimler ve Normal Doku Dozlara Etkileri

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ABSTRACT

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

Methods: We re-planned 10 GBM patients who were previously irradiated. Rigid fusion was performed through pre- and postoperative magnetic resonance imaging (MRI) and simulation computed tomography, and 9 separate volumes were created. While volumes varied from whole brain RT (WBRT) to postoperative two-phase irradiation, RT application ranged from 2-dimensional Co-60 treatment to 3-dimensional volumetric modulated arc therapy (VMAT). OARs were contoured, and doses were noted. A 3 dimensional-conformal RT (3D-CRT) plan of the volume created by preoperative MRI was compared to 3D-CRT and VMAT plans generated by postoperative MRI. Statistical analysis was performed using Paired sample t-test.

Results: During the time of WBRT, normal brain tissue was receiving 45-60 Gy. Through VMAT, the median brain-planning target volume (PTV) Dmean decreased to 35 Gy. According to both PTV-Radiation Therapy Oncology Group (RTOG)preop and PTV-RTOGpostop volumes were noted. A 3 dimensional-conformal RT (3D-CRT) plan of the volume created by preoperative MRI was compared to 3D-CRT and VMAT plans generated by postoperative MRI. Statistical analysis was performed using Paired sample t-test.

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 RTOG, lower normal tissue doses are obtained from VMAT plans, compared to the conformal treatment plans.

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

ÖZ

Amaç: Çalışmanın amacı glioblastoma multiforme (GBM) radyoterapisindeki (RT) geçmiş günümüze değişen eğilimlerin ortaya konulması ve risk altındaki organ dozlardaki değişim göstermesidir.

Yöntemler: GBM tanısı ile postoperatif temozolomid ve RT ile tedavi edilen 10 hastanın simülatörlüğünde bilgisayarlı tomografi görüntülerini retrospektif olarak incelediklerim pre- ve postoperatif manevi rezonans görüntüler (MRG) ile rjjid fusion yapıtıldı ve 9 ayrı volüm oluşturuldu. Volümler total kranyum uygulandığı postoperatif iki fazlı uygulama 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) 9 boyutlu olarak belirlendi. Beyin-hedef hacmi planlama (PTV) Dmean, beyn sapi Dmax, göz Dmax, ipsilateral/ kontralateral, kizma Dmax, koklea Dmax, ipsilateral/kontralateral, lakrimal gland Dmax, ipsilateral/kontralateral, lens Dmax, ipsilateral/ kontralateral, pitüiter gland Dmax, dozlanmıştır. 7, 8, 9, 10 planlar (preop MRG’den oluşturulan volümlerin 3B-konformal RT-3B-KRT planları ile postop MRG’den oluşturulan 3B-KRT ve VMAT planları) karşılaştırıldı. Paired sample t-test ile istatistiksel analiz yapıldı.


Sonuç: Tarihli süreçte uygulanan volüm ve normal doku dozlardında belirgin azalma olmuştur. RTOG’nin postoperatif volüm tanımları göre konformal ve VMAT planları karşılaştırıldığında VMAT planlamada daha düşük normal doku dozları edildi.

Anahtar Kelimeler: 3D konformal radyoterapi, yoğunluk ayarlı radyoterapi, glioblastoma multiforme, volumetrik ark tedavi
Introduction
Glioblastoma multiforme (GBM) is the most deadly and frequent primary brain malignancy in adults (1). Since temozolomide was added to adjuvant radiotherapy (RT), the survival rate has improved (2). Standard treatment of GBM includes surgery, RT, and chemotherapy (3-5). RT has been routinely used in the treatment of brain tumors since the 1940s (6). 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 to 3D-CRT and it can minimize treatment-associated side effects (9). The use of proton RT is also increasing (10). Initially, RT for GBM began as whole brain irradiation. The techniques in RT have improved with the development of different doses and applications and with the determination of organs at risk (OARs) and dose limits. The aim of our study was to reveal the changing trends in RT for GBM from past to present 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 following concomitant temozolomide and RT after surgical resection, were selected from patient database of Istanbul University Institute of Oncology Hospital. After the selection, previous basic scans of the patients were called back to the RT simulation station. No patient actually joined to the simulation process and neither names nor any identifying information related to the study population were used. Due to the retrospective and simulative nature of our study, no informed consent and no ethical approval were obtained. However, the study was performed in compliance with the Declaration of Helsinki. A rigid fusion was performed through MIM software version 6.5 (MIM Software Inc., Ohio, USA) using simCT images, pre- and postoperative contrast-enhanced T1 and T2/flair sequences MR images. OARs and dose constraints were determined according to the European Organization for Research and Treatment of Cancer-Advisory Committee on Radiation Oncology Practice guide and the study of Scoccianti et al. (11,12). Optic chiasm, bilateral eyes, bilateral lenses, brainstem, bilateral cochlea, bilateral lacrimal glands, and pituitary gland were determined as the OARs. Brain-planning target volume (PTV) volume was generated through PTV excluded from brain tissue. In two-dimensional planning (2D), fields were manually created using multi-leaf collimators. Two-phase target volumes yielded from pre-operative MR images were determined according to the Radiation Therapy Oncology Group (RTOG) 9710 protocol. The RTOGpreop phase 1 volume contained the volume of contrasted tumor with peripheral edema on preoperative MRI scan plus a 2 cm extra-margin. The RTOGpreop boost volume covered the contrasted lesion (without edema) on the preoperative MRI scan plus a 2.5 cm extra-margin. The RTOGpostop phase 1 volume included the volume of the postoperative cavity and +/- residual tumor in contrast enhanced T1-weighted MRI scans and edema in the postoperative T2-weighted MRI scans plus a 2 cm margin. The RTOGpostop boost volume included the resection cavity +/- residual tumor in contrast enhanced T1-weighted MRI scans plus a 2 cm margin. 2D treatment planning was used to create plans 1 to 6. 3D planning was made in plans 7 to 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 with 3 full rotation VMAT fields with different collimator angles. VMAT doses were prescribed according to ICRU 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-RTOGpreop phase 1, 6 MV energy, phase 1 dose 46 Gy in 23 fr plus boost dose 14 Gy in 7 fr; Plan 7: PTV-RTOGpreop 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-RTOGpostop phase 1, 6 MV energy, 3D-CRT phase 1 dose 46 Gy in 23 fr plus boost dose 14 Gy in 7 fr; Plan 9: PTV-RTOGpostop phase 1, 6 MV energy, VMAT, 46Gy in 23 fr plus boost 14 Gy in 7 fr. Brain-PTV Dmean, brainstem Dmax, bilateral eye Dmax, optic chiasm Dmax, bilateral cochlea Dmean, bilateral lacrimal gland Dmax, bilateral lens Dmax and pituitary gland Dmax doses were recorded. The plans 7, 8 and 9 were compared.

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

Results
Through VMAT, the median brain-PTV Dmean decreased to 35 Gy while all normal brain tissues received 45-60 Gy. At the same time, 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-RTOGpreop and PTV-RTOGpostop had large treatment volumes, 3D-CRT planning was possible using two opposing coplanar fields. There was no statistically significant difference between the two plans for all OARs doses, including brain-PTV phase 1 Dmean and brain-PTVboost Dmean doses. In addition, optic chiasm Dmax, bilateral cochlea Dmean, brainstem Dmax, bilateral lens Dmax, bilateral eye Dmax median dose values were over the dose constraints. The PTV-RTOGpreop 3D-CRT, PTV-RTOGpostop VMAT plans were compared; doses of brain-PTV phase 1 Dmean (median 41.7 Gy vs. 24.1 Gy, p=0.001), brain-PTVboost Dmean (median 44 Gy vs 34.4 Gy, p=0.021), chiasm Dmax (median 62.1 Gy vs. 52.9 Gy, p=0.030), contralateral cochlear Dmax (median 59 Gy vs. 13.8 Gy, p=0.002), ipsilateral cochlear Dmax (median 61 Gy vs. 28.5 Gy, p=0.006) and contralateral eye Dmax (median 36.2 Gy vs. 23.2 Gy, p=0.022) were statistically lower in the RTOGpostop VMAT plan. The lens Dmax doses were within dose constraints except for one value in both groups, although the RTOGpostop VMAT dose was higher in the lens Dmax dose (median 3.9 Gy vs. 7.9 Gy, p=0.005). The PTV-RTOGpostop 3D-CRT plan was compared to PTV-RTOGpostop VMAT; the doses of Brain-PTV initial Dmean (median 43.5 Gy vs. 24.1 Gy, p<0.001), brain-PTV boost Dmean (median 45.5 Gy vs. 34.4 Gy,
p=0.007), and contralateral lacrimal gland D max (median 36.4 Gy vs. 46.7 Gy, p=0.005), contralateral eye D max (median 40.1 Gy vs. 23.2 Gy, p=0.0232) were statistically lower in the RTOG postop VMAT plan. To the RTOGpostop 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). We found that all the OARs and whole brain tissue received a median [standard deviation (SD)] dose of 45.3 Gy, except for lenses, 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 protected with protection blocks anatomically because of being away from the brain tissue. In 1979, Walker et al. (13) found that 50-60 Gy doses were associated with increased survival when compared with doses ≤45 Gy. In those days, 50-60 Gy was applied to the whole brain. When we performed 60 Gy 2D WBRT with Co-60 and linear accelerators, we found that all the OARs and the whole brain were receiving a median (SD) dose of 60.8 Gy, except for the lenses. All of the OARs exceeded the dose constraints that need to be considered today. 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, so 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). Afterwards, 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) + boost (20 Gy/10 fr), PTV-RTOG prog phase 1 (46 Gy/23 fr) + PTV-RTGBoost (14 Gy/7 fr) volumes generated according to RTOG 9710. Between these two plans, there were no significant differences in terms of Brain-PTVinitial D_max, optic chiasm D_max and brainstem D_max doses. However, in the plans generated according to RTOG 9710, the brain-PTV boost D_max, contralateral cochlear D_max, contralateral eye D_max, contralateral lacrimal gland D_max, ipsilateral lacrimal gland D_max, ipsilateral lens D_max, and ipsilateral lens D_max doses were significantly lower, so normal OARs were better spared. 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 RTG 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 RTG and MD Anderson Cancer Center plans, they revealed that 90% of the recurrences were central and within the area. Today, guidelines recommend using a postoperative MRI while defining/delineation target volume for RT in GBM. Different cooperative groups have target volume delineation that includes or excludes peritumoral edema (26). In this 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-RTG prog and PTV-RTG prog volumes, and the OARs doses, made in two phase VMAT plan according to the RTOG prog volume, are given in Table 1.

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

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References


