ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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EFFECT OF TARGET DELINEATION AND DOSE PARAMETERS ON LOCAL FAILURE PATTERN AFTER ADJUVANT RADIOTHERAPY IN GLIOBLASTOMA: EVALUATION OF EORTC AND RTOG GUIDELINES

GLİOBLASTOMA OLGULARINDA HEDEF BELİRLENMESİ VE DOZ PARAMETRELERİNİN ADJUVAN RADYOTERAPİ SONRASI LOKAL NÜKS PATERNİ ÜZERİNE ETKİSİ: EORTC VE RTOG KILAVUZLARININ DEĞERLENDİRİLMESİ

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Öz

Amaç

Çalışmamızın amacı glioblastoma (GBM) tanısı ile adjuvan radyoterapi (RT) eş zamanlı temozolamid uygulanmış olan hastalarda nüks paterninin doz dağılımı ile ilişkisinin değerlendirilmesidir. Buna ek olarak çalışma sonuçlarının ışığında GBM olgularında RT hedef belirlenmesinde kullanılan European Organisation for Research and Treatment of Cancer (EORTC) ve Radiation Therapy Oncology Group (RTOG) kılavuzları tartışılması amaçlandı.

Gereç ve Yöntem

Kliniğimizde, biyopsi veya cerrahi eksizyon sonrası GBM tanısı almış ve Ekim 2011 – Haziran 2018 tarihleri arasında adjuvan RT eş zamanlı temozolamid uygulanmış 31 hasta çalışmaya alındı. Radyoterapi 22 hastaya 3 boyutlu konformal, 9 hastaya ise yoğunluk ayarlı RT tekniği ile 46 Gy (Faz I) sonrası 14 Gy boost (Faz II) olmak üzere toplam 60 Gy şeklinde uygulandı. Tüm hastalar RT eş zamanlı 75 mg /m2/ gün temozolamid aldı. Hastaların radyoterapi öncesi iki hafta içerisinde çekilmiş olan MR görüntüleri baz olarak alındı. Radyoterapi sonrası 2-3. ay veya sonrasındaki kontrol T1 MR görüntülerinde operasyon kavitesi veya postoperatif rezidüel lezyonun kontrast tutulumunda artış, kontrast tutan volümde artış, T2/ FLAIR görüntülerde ödemde artış olan hastalar progresyon olarak değerlendirilirken operasyon kavitesi veya postoperatif rezidüel lezyondan ayrı, yeni gelişen lezyonlar nüks olarak kabul edildi. Nüks lezyonlar uzman radyolog tarafından MR spektroskopi görüntüleri üzerine konturlandı. Bu görüntüler planlama CT görüntüleri ile füzyon yapılarak nüks lezyon alanının retrospektif dozimetrik değerlendirilmesi yapıldı. Dozimetrik incelemede nüks lezyon alanının maksimum, minimum ve ortalama dozları, D95(%95 inin aldığı doz), D50 (%50 sinin aldığı doz), V%95 (planlanan dozun %95 ini alan volüm) değerlendirildi.

Bulgular

Çalışmaya alınan 31 hastanın ortalama yaşı 59 yıl (28 -78) olup median takip süresi 17 (5 -64) aydır. Median genel sağkalım 17 (5 - 66) ay olarak bulundu. Operasyon 19 hastada GTR, 10 hastada STR şeklinde olup 2 hasta biyopsi ile tanı almış idi. Bir hasta hariç tüm hastalarda postoperatif MR görüntülerinde rezidü

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mevcut idi. Takip süresinde 1 hastada progresyon, 14 hastada nüks saptanırken 16 hastanın stabil olduğu gözlendi. Nüks olan 12 hastada lezyon %100 oranında PTV60 içinde yer almakta iken kalan iki hastada bu oran sırasıyla %98.7 ve 61.8 idi. Ortalama nüks volümü 11.14 (0.7 – 48) cc olarak bulundu. Nüks lezyonların ortalama maksimum, minimum ve mean dozları, D95, D50, V%95 sırasıyla 6246 cGy (6043 – 6439), 5805 cGy (3574 – 6098) ,6106 cGy (5906 – 6223), 5941 cGy (4588 – 6162), 6123 cGy (6009 – 6217), 11,04 cc (0.7 – 48.37) idi.

Sonuç
Çalışmamızda rekürren lezyonların % 95 oranında PTV 60 içerisinde olduğu görüldü. Bu sonuç baz alındığında, ödem alanını içeren hedef volüme faz I olarak 46 Gy uygulanmasının katkısı tartışmalıdır. Özellikle operasyon kavitesi ve rezidü boyutu büyük olan ve normal doku toksistesinin yüksek olacağı öngörülen hastalarda tek fazlı tedavi tercih edilebilir.

Anahtar Kelimeler: Glioblastoma, hedef belirleme, lokal nüks özellikleri.

Abstract

Objective
We aimed to investigate the correlation between dose distribution and relapse pattern in glioblastoma patients who underwent adjuvant radiotherapy (RT) and to discuss European Organisation for Research and Treatment of Cancer (EORTC) and Radiation Therapy Oncology Group (RTOG) guidelines commonly used for target volume delineation.

Materials and Method
Thirty-one consecutive glioblastoma patients who underwent adjuvant concomitant chemoradioterapy (temozolamide) after biopsy or surgical resection in our clinic between October 2011 and June 2018 were enrolled. Total dose of 60 Gy with 14 Gy boost after 46 Gy RT was given with 3 dimensional conformal (3DCRT) in 22 patients and intensity modulated technique (IMRT) in 9 patients. All patients were administered concomitant temozolamide 75 mg/m2/day. The MR images taken within 2 weeks before RT is considered as basal investigation. Recurrent lesions in control MR spectroscopy images within 2-3 months after RT were retrospectively contoured by a radiologist and fused with planning CT images. Increase in contrast enhancement and enhanced volume in T1 MR sequences or increase in edema in T2/FLAIR sequences is reported as progression. Recurrence is defined as new emerged lesions apart from resection cavity or known postoperative residual lesion. The fused images are evaluated dosimetrically to calculate D95 (Dose of %95 volume), D50 (Dose of %50 volume), V%95 (volume receiving % 95 of planned dose) of recurrent area.

Results
Median age of patients was 59 (28 -78) years with a median survival of 17 (5 - 66) months in 17 (5 -64) months of median follow up. Median overall survival was found to be 17 (5 - 66) months. GTR, subtotal resection (STR) and biopsy were performed in 19, 10 and 2 patients respectively. All but one patient had residual mass in the postroperative images. During follow up 1 patient progressed whereas 16 patient was stable. Recurrence was detected in 14 patients. Whole volume of recurred lesions was in PTV60 in 12 patients. In the remaining 2 patients, volume of recurrent lesion in PTV60 were 98.7 and 61.8 % respectively. Mean recurrent volume was found 11.14 (0.7 – 48) cc. The mean of maximum, minimum and mean doses were 6246 cGy (6043 – 6439), 5805 cGy (3574 – 6098) and 6106 cGy (5906 – 6223) respectively.

Conclusion
In our study 95% of the recurrent lesions were in PTV 60. In our opinion, the contribution of 46 Gy to edema, especially for patients with a large operation cavity and residual lesion which could cause high normal tissue toxicity is controversial. Therefore, single phase treatment is reasonable in these patients.

Keywords: Glioblastoma, target delineation, local failure pattern

Introductıon

Glioblastoma (GBM) is the most aggressive diffuse glioma of astrocytic lineage and is considered as grade IV based on the WHO classification (1) almost always with poor prognosis (2). Current standard of care is gross total resection (GTR) of the contrast enhancing tumor followed by concurrent chemoradiotherapy (CRT) with temozolomide continued with adjuvant temozolomide (3-5). Nevertheless, median survival raised to 15–16 months from 9-12 months with abovementioned standard of care (6,7), and reported 5-year survival rate is about 10.8% (8). A maximal safe resection of the enhancing tumor is the preferred surgery however, in patients with predicted high risk of major functional impairment, an open or

stereotactic biopsy is compulsory (9). Whole-brain radiotherapy (WBRT) with or without tumor directed boost to improve local control have been used to treat GBM patients in the past (10). However, close proximity to radiosensitive organs at risk (OARs) and proven detrimental effect of high dose RT on cognitive functions necessitated new developments on radiotherapy treatment planning and fractionation such as stereotactic radiosurgery, hypofractionation and hippocampal avoidance (11-13). For this purpose, two phase partial brain irradiation was defined as a first step. Consequently, sophisticated focal radiotherapy techniques such as 3D-CRT, intensity modulated radiotherapy (IMRT) and volumetric intensity modulated arc therapy (VMAT) were introduced. With the increasing utilization of computerized tomography (CT) for radiotherapy planning, and technological improvement, an accurate target volume delineation for more conformal Planning Target Volume (PTV) has come into prominence. Plenty of studies aiming to define the optimal treatment volume for the malignant gliomas are reported (2, 14, 15). Consequently, two major guidelines exist in parallel. European Organization for Research and Treatment of Cancer (EORTC) recommend including the surgical resection cavity and any residual enhancing tumor defined on post-contrast T1 weighted MRI scans plus a 2 cm margin in clinical target volume (CTV) up to a total RT dose of 60 Gy in 30 fractions (5,16). On the other hand, Radiotherapy and Oncology Group (RTOG) recommends a 2-phase approach including an initial field prescribed to 46 Gy which is peritumoral edema defined on T2-weighted or Fluid Attenuated Inversion Recovery (FLAIR) scans added to the resection cavity and any residual enhancing tumor plus a 2 cm margin followed by an additional boost prescribed to GTV + 2.5 cm a to total dose of 60 Gy all in 2 Gy fractions (17-20). ESTRO Advisory Committee on Radiation Oncology Practice (ESTRO-ACROP) suggested another delineation allowing adaption of previously defined CTV per EORTC to include the adjacent FLAIR hyper intensities in some cases (19). Although the relation between peritumoral edema and local recurrence pattern is not clearly proven yet, including peritumoral edema in the initial phase volume is mainly based on the belief that these areas contain high concentrations of tumor cells largely defined by postmortem histological findings and tumor recurrence analyses (21-23). For instance, 80% or 95% of recurrences were reported to be within 2 - 3 cm around the resection cavity (21,24,25). According to some investigators peritumoral edema is directly caused by infiltrating tumors cells, where some others believe that this is just a spatial coincidence of peritumoral edema and infiltrating tumor cells. The most important drawback of this approach is larger radiation treatment fields which means larger volume of normal brain tissue exposed to high dose radiation (24, 26-29). Noteworthy that, tumor cells were found in a large brain volume infiltrating via white matter tracks (21, 30).

In this study we aimed to evaluate the impact of target volume delineation and dose distribution parameters on recurrence pattern in glioblastoma patients underwent adjuvant radiotherapy. Additionally, we discussed the EORTC and RTOG suggestions for target volume delineation in these patients on the basis of our results.

Materials and Methods

Thirty-one consecutive patients who underwent adjuvant concomitant chemoradioterapy (temozolomide) for GBM in our clinic between October 2011 – June 2018 were enrolled. Due to the time period of our study patients treated before 2016 when WHO proposed a new classification (1) were pathologically recorded as glioblastoma multiforme. According to the WHO classification for CNS tumors on 2016, GBM is divided into the following groups: (a) GBM, IDH-wild type (about 90% of cases) which is most frequently defined as primary or de novo GBM and predominantly seen over 55 years, (b) GBM, IDH-mutant (about 10% of cases) mostly seen as GBM secondary to prior lower grade diffuse glioma and occurring in younger patients. (c) GBM, NOS, used for tumors which full IDH evaluation cannot be performed. (1,31,32).

All patients were given temozolamide 75 mg/m2/day concomitantly. The study was approved by the Scientific Research Ethics Committee of Medical Faculty of University (protocol code, 2019/48). All procedures performed in terms of the ethical standards of the institutional research committee in alliance with the 1964 Helsinki declaration and its later amendments. Informed consent was waived owing to the retrospective nature of the study.

Radiotherapy

All patients were treated according to ESTRO-ACROP consensus guidelines (19). Planning tomography was performed via GE Bright Speed Excel Select 4 CT simulator with 2.5 mm slice thickness. A thermoplastic mask was done for immobilization to all patients before planning tomography. Eclipse Version 10, (Varian Medical System, Palo Alto, CA) was used for treatment planning. Magnetic resonance (MR) images transferred from image archive of our hospital via Picture Archiving Communication Systems (PACS) of our hospital were fused with planning tomography im-

ages. Radiation treatment was given with 3DCRT (22 patients) or IMRT (9 patients) to phase I volume as 46 Gy and an additional 14 Gy boost (phase II) to a total dose of 60 Gy. 6 MV and/or 18-MV photon energy was chosen according to dose distribution, target volume and localization parameters.

Target volumes were defined as;

Phase I: Gross tumor volume (GTV)1: Residual volume apparent in T1 contrast enhanced MR images + postsurgical cavity + edema seen in T2/ FLAIR images

CTV1: GTV + 2 cm

Planning target volume (PTV) 1: CTV + 0.5 cm

Phase II (Boost): GTV2: Residual volume apparent in T1 contrast enhanced MR images + postsurgical cavity

CTV2: GTV + 2 cm

PTV2: CTV + 0.5 cm, according to RTOG suggestion. Target volumes are shown as schematic diagrams in Figure 1.

The hyperintensity region in FLAIR sequences was included in the CTV if it was out of CTV expansion. And CTVs were manually adapted to anatomic structures per ESTRO-ACROP consensus guidelines (19).

Radiologic evaluation of recurrence

Postoperative MR images taken within 2 weeks before radiation treatment was regarded as basic exam for further comparative evaluations. These images were compared with T2, FLAIR, contrast enhanced T1, diffusion weighted, MR spectroscopy and perfusion images done 2-3 months after radiotherapy or later by 2 radiology specialists. Areas defined as recurrence are contoured in axial and coronal plans of T1 and T2 contrast enhanced images by the same radiologists. Retrospective dosimetric evaluation of recurrent area was performed on the fusion images of contoured MR and planning tomography (Figure 2). Parameters calculated in dosimetric evaluation were maximum, minimum and mean doses, D95(dose in 95% volume), D50(dose in 50% volume), V%95 (volume exposed to 95% of prescribed dose) in recurrent area. Subvolumes were defined for further dosimetric analysis. These volumes are shown as schematic diagrams in Figure 3. Recurrence was defined as central in cases where more than 95% of recurrent area is in PTV 60, in-field if 80–95% is intersecting with PTV 60, marginal when this ratio is 20–80% and distant when it is <%20 (25).

Statistics

Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) 22.0 for Windows. Overall survival analysis was calculated via Kaplan-Meier method.

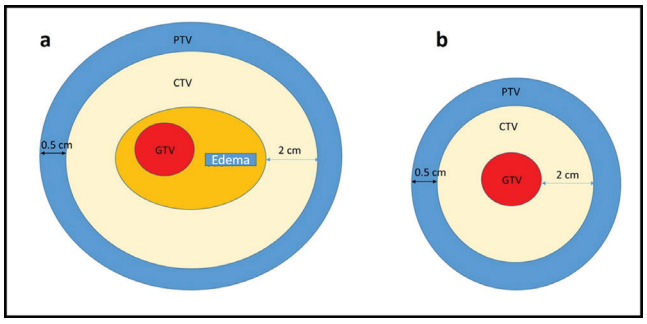

Figure 1
Phase I (a) and II (b) target volume definitions according to RTOG 97-10 protocol.

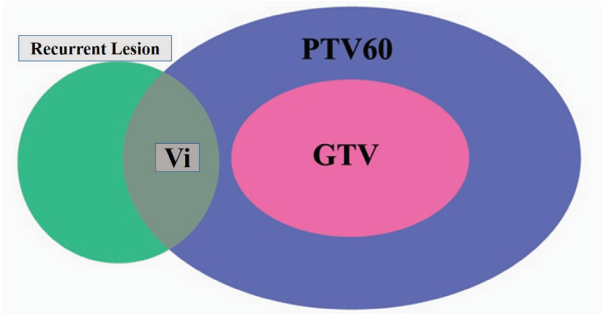

Figure 3
PTV60: Target volume for Phase II/60 Gy, Vi: Intersecting volume between PTV 60 and recurrent lesion

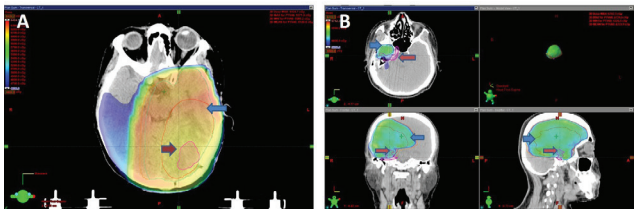

Figure 2
Recurrent lesion (red arrow) totally in maximum phase II dose region (60 Gy/blue arrow), central recurrence (A), recurrent lesion (red arrow) 68% in phase II dose region (60 Gy/blue arrow), in-field recurrence (B).

Table 1 Maximum, minimum and mean doses, D95, D50, V%95 values in recurrent area

	Mean (Min – Max)
Recurrent volume	11.14 (0.7 – 48) cc.
Maximum	6246 cGy (6043 – 6439)
Minimum	5805 cGy (3574 – 6098)
Mean	6106 cGy (5906 – 6223)
D95	5941 cGy (4588 – 6162)
D50	6123 cGy (6009 – 6217)
V 95%	11,04 cc (07 – 48,37)

Results

Median age of whole group was 59 (28 -78) years. Median overall survival (OS) was found 17 (5 - 66) months in a 17 (5 -64) months' follow up. Tumors were located in right frontal, right parietal, left frontal, left parietal and left occipital lobes in 6,11,1,9 and 4 patients respectively.

GTR was achieved in 19 patients where 10 patients underwent subtotal resection (STR) and remaining 2 had biopsy only. All but one patient had residual tumor in postoperative MR images. On follow up 1 patient had progression, 14 patients had recurrence and 16 patients were regarded as stabile disease. Recurrences were central, in-field and marginal in 12,1 and 1 patients respectively. Volume of recurrent lesion intersecting with PTV 60 in 2 latter patients were 98.7 and 61.8 % respectively. Mean recurrent volume was 11.14 (0.7 – 48) cc.

Maximum, minimum and mean doses, D95, D50, V%95 in recurrent area are shown in Table 1.

Discussion:

With the increasing utilization of CT for radiotherapy planning, plenty of studies aiming to define the optimal treatment volume for the malignant gliomas are reported (2,14,15).

According to the ESTRO-ACROP guidelines the GTV consists of the surgical cavity and any residual contrast enhancement on T1-weighted MRI (19). To include microscopic disease, the GTV is isotropically expanded by 2 cm to obtain CTV. The CTV is then adapted manually to anatomical barriers. This target delineation algorithm seems to be general approach seems appropriate considering that 80% of the recurrences are central and 95% within the radiation field (33,34). However, this method has some insufficiencies particularly in certain subgroups whose non-central recurrences can be up to 40% (34,35) and accurate prediction of recurrence localization (also within the 2 cm margin) is still impossible due to the heterogeneity of this disease.

Hyperintense area around the tumor in T2 MR images consists of tumoral infiltration and vasogenic edema which is called "peritumoral edema" (36). Especially peritumoral edema seen in high grade gliomas is attributed to damaged blood brain barrier (BBB). Inclusion of peritumoral edema within the CTV is still a matter of debate in adjuvant radiotherapy planning for glioblastoma. In the previous and current protocols of RTOG it is suggested to include peritumoral edema in the CTV (18), however, some other reference centers such as MD Anderson (37) do not include edema in glioblastoma target volume in their daily practice. Herein, we investigated the impact of peritumoral edema on local recurrence pattern and necessity of including peritumoral edema in CTV.

The investigators supporting to include edema, based on a theory of atypical cells exceeding the peritumoral edema region (21, 38,39). Opposing researchers speculate that the proximity to the gross tumor is the main factor creating recurrence pattern in malignant gliomas (28, 40). Hochberg and Pruitt (27), reported that 80% of glioblastoma patients recurred within 2 cm of the margin of the primary tumor bed by analyzing CT data after whole-brain radiotherapy which was confirmed with the similar results in the studies by Wallner et al (24) and Liang et al (26). Another study (40) with 36 high grade astrocytoma patients reported 89% central or in-field recurrence. In a related investigation by the same group, radiotherapy dose increased to 90 Gy and 91% of recurrences were cen-

tral or in-field (41,42). Chang et al. (37), formed a virtual plan for 48 recurrent glioblastoma cases in their study which they redefined the target volumes according to RTOG. No correlation was found between recurrence localization and peritumoral edema volume via linear regression model [r2=0.0007; p= 0.3]. In the same study, normal brain tissue exposed to 46 Gy was significantly larger in patients with edema volume >75 cm3 (38% vs. 31%; p = 0.003). Recurrence pattern (40 central, 3 in-field, 2 distant) was similar in both plans. Conclusively, especially in patients with large peritumoral edema volume CTV formed with 2 cm margins to GTV is suggested as an adequate and less toxic approach. Similarly, in our study, treatment plan is reevaluated in terms of dose to recurrent area and recurrence pattern was seen as 12 central, 1 in-field and 1 marginal.

RT planning studies showed major differences in GTV definition depending on MRI technique (19,43,44). Whole Brain Spectroscopy may assess tumor infiltration related to GBM tumor cell density (45) and the CTV is adjusted using estimated tumor cell density by a mathematical modeling of tumor growth (46). Several alternative imaging approaches have also been advocated to optimize target delineation in GBM radiotherapy planning. A tumor growth model using (18) F-fluoro-ethyl-tyrosine PET biological tumor volumes is demonstrated (47). Amino acid-based positron emission tomography (PET) uptake can be used to assess the cancerous metabolism and improve postoperative gross tumor assessment (48.49).

In high grade gliomas, an increase in tumor size, contrast enhancement determined in control images but not in concordance with clinical status which is seen soon after radiochemotherapy so called “pseudoprogression” can be easily mixed with recurrence. The differential diagnosis is important to guide treatment strategy but unfortunately conventional imaging techniques and sequences are mostly inadequate. In case of progression, contrast enhancement features and enlargement persist in 6 months’ control images (50,51). Corpus callosum invasion, lesion crossing midline, multiple contrast enhanced lesions not crossing midline or subepandymal invasion are also strong signs of progression. Some special modalities such as SWI sequence sensitive to microvascularity, hemorrhagic inclusion and iron inclusion of the tumor (52,53), DWI sensitive to thermal energy and random movements of water molecules and diffusion coefficient (ADC) can provide higher accuracy in detection of recurrence (54). Decreasing ADC in DWI, increasing choline/creatinine or choline/NAA ratios in spectroscopy, increasing rCBV in perfusion may usually support recurrence.

Another important entity of differential diagnosis is radionecrosis which is frequently seen after high doses of adjuvant radiotherapy in high grade gliomas. Radionecrosis can be seen as an edema or mass effect in T2/FLAIR in early phase and as a volume defect in late control images.

Single or multiple nodular or curvilinear cavitary areas with irregular peripheral contrast enhancement in contrast enhanced T1 images resembling “soap bubble” or “Swedish cheese” sign also indicates radionecrosis (55).

The most important limitation of our study is the small sample size despite relatively long follow up time. The other important handicap is the lack of pathologic proof of recurrent lesions which was usually avoided due to poor performance status of the patient or ethical considerations.

Conclusion

In target delineation for glioblastoma patients, mostly used EORTC and RTOG guidelines have different suggestions. Taking the increasing probability of consequential neurological dysfunctions into consideration, the contribution of prescribing initial 46 Gy to phase I target volume including edema is controversial. Confirming the adequacy EORTC suggestions, in our study we found that all the recurrent lesions were in or very close to PTV 60. Therefore, we suggest single phase treatment especially in patients with large operation cavity or residual tumor who have increased risk of late complications due to large treatment volumes.

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