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Research Article

Retrospective Clinical and Radiologic Analysis of Adult High-Grade Glioma Recurrence After Temozolomide-Based Radiochemotherapy

Burcu AKBELEN[1], Serra KAMER[1], Cem CALLI[2], Sinan HOCA[1], Yavuz ANACAK[1]

[1]Ege University, Radiation Oncology, İzmir, Turkey [2]Ege University, Radiology, İzmir, Turkey

Summary

Background: The aim of this study was to evaluate the recurrence patterns and the times of recurrence after temozolomide-based radiochemotherapy for high grade gliomas.
Methods: Magnetic resonance imaging (MRI), diffusion MRI, perfusion MRI, and MRI spectroscopy scans of 30 patients who were treated with radiotherapy concurrently with temozolomide chemotherapy between June 2009 and April 2012 were retrospectively evaluated. Central, in-field, marginal, and distant recurrences of progression were defined related to radiation therapy dose distribution (90% isodose line).
Results: The overall survival (OS) rates of central recurrences at 1 year and 2 years were 78% and 25%, respectively (at a median of 16 months). The OS rate of in-field, marginal and distant recurrences at 1 year and 2 years were 100% and 40%, respectively (at a median of 24 months). The progression-free survival (PFS) rate of central recurrences at 1 year and 2 years were 21% and 0%, respectively (at a median of 5 months). The PFS rate of in-field, marginal and distant recurrences at 1 year and 2 years were 36% and 27%, respectively (at a median of 11 months). The PFS rate of pseudoprogression at 1 year and 2 years were 87% and 43% (range, 7-31 months).
Conclusions: The survival of new in-field, marginal and distant recurrences are longer and these new lesions develop at a later time compared with central recurrences. Pseudoprogression predicts better response to temozolomide-based radiochemotherapy. Finally, the location of recurrence is determined as one of the prognostic factors for OS and PFS.

Key words: Glioblastoma, radiochemoterapy, temozolomide, recurrence, pseudoprogression

Yetişkin Yüksek Dereceli Gliom Olgularinin Radyokemoterapi Sonrasi Yinelemelerinin Klinik ve Radyolojik Değerlendirilmesi

Özet

Amaç: Bu çalışmanın amacı yüksek dereceli gliom olgularının temozolomid ile eşzamanlı radyokemoterapi sonrası yineleme paternlerini ve sürelerini değerlendirmektir.
Metod: Haziran 2009- Nisan 2012 tarihleri arasında Ege Üniversitesi Tıp Fakültesi Radyasyon Onkolojisi kliniğinde yüksek dereceli gliom tanısıyla temozolomid ile eşzamanlı radyokemoterapi programına alınan, tedavi sonrası takip amaçlı yapılan manyetik resonans görüntüleme (MRI), diffüzyon MRI ve MRI spektroskopi tetkiklerinde progresyon saptanan 30 olgu klinik ve radyolojik yineleme özellikleri açısından geriye yönelik olarak değerlendirilmiştir. Santral, saha içi, marjinal ve saha dışı yinelemeler, primer tümörün radyoterapi planındaki radyoterapi doz dağılımına göre (%90'lık izodoz eğrilerine) tanımlanmıştır.

Bulgular: Santral yineleme saptanan 14 olgunun 1 ve 2 yıllık genel sağkalımları sırası ile %78 ve %25 (medyan 16 ay); sadece saha içi, saha dışı veya marjinal yineleme saptanan 11 olgunun 1 ve 2 yıllık genel sağkalımları sırası ile %100 ve %40 (medyan 24 ay) olarak tespit edilmiştir. Santral yineleme saptanan 14 olgunun 1 ve 2 yıllık progresyonsuz sağkalımları %21 ve %0 (medyan 5 ay), sadece saha içi, saha dışı veya marjinal yineleme saptanan 11 olgunun 1 ve 2 yıllık progresyonsuz sağkalımları %36 ve %27'dir (medyan 11 ay). Psödoprogresyon saptanan 8 olgunun 1 yıllık ve 2 yıllık progresyonsuz sağkalımları %87 ve %43'tür (7-31 ay).
Sonuç: Santral yinelemeler ile karşılaştırıldığında; saha içi marjinal ve saha dışı yineleme saptanan olguların sağkalımları daha uzundur ve daha geç zamanda ortaya çıkmaktadır. Psödoprogresyon gelişimi temozolomid bazlı radyokemoterapiye iyi yanıtın göstergesidir. Sonuçta, yinelemelerin lokalizasyonlari genel ve progresyonsuz sağkalım için bir prognostik faktör olarak kabul edilmiştir.

Anahtar Kelimeler: Glioblastom, radyokemoterapi, temozolomid, yineleme, psödoprogresyon

INTRODUCTION

Primary central nervous system tumors account for 1.4% of all cancers. Primary brain tumors are the cause of 2.2% of cancer deaths (1). High-grade gliomas comprises 77% of malignant brain tumors and glioblastoma (GBM), consistitutes 82% of tumors histopatologically (2). Despite the progress of treatment strategies, median survival is around 2 years.

For patients with GBM, it is proven that postoperative fractionated radiotherapy (RT) concurrent with temozolomide (TMZ) and adjuvant TMZ treatment for six months clearly improves overall survival (3,4). In the European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada (EORTC/NCIC) randomized trial, chemotherapy added to RT prolonged overall survival to 14.6 months from 12.1 months (5).

For the assessment of high-grade glioma treatment, overall survival (OS), radiologic response, and progression-free survival (PFS) are significant factors. However, most patients have recurrence in the first months after TMZ-based radiochemotherapy, 15-30% of these were established as lesions mimicking progression (6-10).

Improved radiologic modalities such as diffusion magnetic resonance imaging (MRI), perfusion MRI, MRI spectroscopy, positron emission tomography-computed tomography (PET-CT) for the differentiation of progression from pseudoprogression and radionecrosis can help to maintain the treatment of recurrence (11). After whole brain radiotherapy or conformal radiotherapy, local recurrence appears mostly in the area of 2 cm around the original tumor (12-19). The conformal RT volumes of the contrast enhancing tumor and the peritumoral edema are standard. The total dose is 60 Gy (20,21). Raising the dose to 90 Gy or stereotactic radiosurgery (SRS) boost achieves a high-dose volume but local recurrence beyond the high-dose region cannot be avoided (22-24).

In this study, analysis of the recurrence locations of patients with newly diagnosed high-grade glioma after TMZ-based radiochemoterapy was performed, and the effect of TMZ-based radiochemotherapy on recurrence patterns was investigated.

MATERIAL AND METHODS

Patient characteristics and treatment

MRI, diffusion MRI, perfusion MRI and MRI spectroscopy scans of 30 patients who were treated with radiotherapy, concurrently with TMZ chemotherapy between June 2009 and April 2012, were retrospectively evaluated. All patients

underwent biopsy or resection to define the pathologic diagnosis of high-grade glioma. The patients in this study developed at least one radiologic progression after radiochemotherapy in the follow-up MRIs.

Patients were simulated and irradiated using a thermoplastic mask for immobilization. Computed tomography was used for simulation. XIO software was used for the 4 patients in radiotherapy planning, and Precise software was used for the other 26 patients. For optimization and the fusion of the progressed radiologic images, all plans made using Precise were identically copied to XIO. The study data were obtained from the XIO.

Gross tumor volume (GTV) was defined according to the preoperative contrast enhancing T1 MRI images. Clinical target volume 1 (CTV1) was formed as GTV plus 2 cm margin (bone structures and regions that were not considered in relation with tumor were excluded). PTV1 was formed as CTV1 plus 0.5 cm margin, which received 50 Gy (2Gy/fx, 25 days). CTV2 was performed as GTV plus 1 cm margin. PTV2 was formed as CTV2 plus 0.5 cm margin, which recieved a 10 Gy boost dose (2 Gy/fx, 5 days).

As long as the performance status was good or there was no toxicity of chemotherapy or no progression, patients regularly received concurrent 75 mg/m^2/day TMZ pills and adjuvant TMZ pills at a dosage of 150-200 mg/m^2/day for 5 days every 28 days for a one-year period.

Analysis of recurrence patterns

Follow-up MRI was performed at the first month after radiotherapy and every 2 or 3 subsequent months. The last follow-up date was in November 2012. Treatment response criteria were evaluated according to the revised Macdonald criteria (25). For the differentiation of progression from pseudoprogression and radionecrosis, conventional MRI, diffusion MRI, perfusion MRI and MRI spectroscopy were performed.

If the tumor image had progressed at the first follow-up (4-6 weeks) and was still progressing at the next follow-up screening, we defined it as true progression; if it was stable or regresing, we defined it as pseudoprogression (10,26,27).

Progression was classified as being central, in-field, marginal, and distant recurrence as in Milano et al's 2009 study (28). Central recurrence was defined as the original tumor growing or the lesion appearing in the operation cavity. In-field recurrence was defined as a new lesion appearing completely in the 90% isodose line, marginal recurrence was defined as a new lesion crossing the 90% isodose line, distant recurrence was defined as the new lesion appearing outside the 90% isodose line. The volume of recurrent lesions was measured and evaluated by their location.

Overall survival refers to the time from the date of surgery to death or the last follow-up date. Progression-free survival refers to the time from the date of surgery to date of progression as viewed in MRI.

The statistic analysis was performed using IBM SPSS Statistics Version 20 software. $P \leq 0.05$ was accepted as statistically significant. Overall survival and PFS were calculated using Kaplan-Meier analysis, and the log-rank test was used for univariate analysis. Recurrent volumes were evaluated using Spearman"s correlation test. This study was approved by the local ethics commity of Ege University.

RESULTS

The 30 patients with recurrence who were included in this study were assessed in December 2012 (median follow-up time: 18.9 months). The median age was 52.5 years (range, 18-70 years). The ratio of women to men was 11:19. Gross total resection was performed for 20 patients (66.7%), subtotal resection for 9 (30%) and stereotactic biopsy for one (3.3%). According to the first MRI, 3 patients had multiple paranchimal tumors.

Twenty-four patients were treated with concurrent TMZ regularly; 6 patients could not continue with chemotherapy because of

thrombocytopenia. Eleven patients (36%) had adjuvant TMZ for 12 cures; 9 patients (30%) for 6-11 cures and 1 patient (3.3) had no TMZ due adverse effects or disease progression. In the follow-up period, 7 patients (23.3%) had radionecrosis, 4 patients (13.3%) had leucoencephalopathy, and 3 patients (10%) had both.

Three of 10 patients (30%) underwent surgery for hystopathologic examination to determine radionecrosis, which resulted as necrosis but also tumor cells were seen. No pure necrosis was hystopathologically reported. For the other 7 (70%) patients, radionecrosis was determined in radiologic examinations. The mean radionecrosis time after RT completion was calculated as 9.5 months (range, 1-36 months).

Reccurence patterns

In the median follow up time, 8 of 30 (26%) patients had pseudoprogression (median: 4 months, range, 3-6 months). Although 5 of 8 had no progression, 3 of 8 progressed after a median time of 14 months (range, 7-21 months).

The 14 patients (56%) who progressed had central recurrence (median: 5 months, range, 3-21 months). Three of these patients were those who had pseudoprogression in the first or second follow-up after RT (median 3: months, range, 3-6 months). One patient who had pseudoprogression in the 3rd month also had central recurrence and in-field recurrence in 21st month. Another patient who had central recurrence in the 4th month had in-field recurrence in the 7th month, one patient who had central recurrence in 3rd month developed marginal recurrence at the same time and one patient who had central recurrence in the 5th month had simulatneous distant recurrence.

Seven (28%) of 25 patients who progressed had only in-field recurrence (median: 12 months, range 4-40 months). Three (12%) of the 25 patients with progression had only marginal recurrence (median: 11 months, range, 4-13 months). One (4%) of the 25 patients with progression had only distant reccurrence in the 5th month (Figure 1).

When the volume of recurrence was evaluated, we calculated that the mean and median volume of central recurrence (14 patients) was 32.9 cc and 47.5 cc, respectively; the volume of only in-field, marginal and the mean and median distant recurrence (11 patients) was 21.8 cc and 7 cc, respectively. The volume of central recurrences (local progression) was determined to be larger than the volume of in-field, marginal and distant recurrence.

Eight (66.6%) of 12 patients who progressed in 12 weeks after the completion of RT had recurrent lesions within the D80 isodose line, and 4 patients of 12 had recurrent lesions outside the D80 isodose line. Two (25%) of 8 patients who had pseudoprogression had lesions 5 months after RT, 2 patients had pseudoprogression 2 months after RT, 3 patients (37%) had pseudoprogression 1 month after RT. Five patients of 6 who had pseudoprogression within 12 weeks of completing RT had their lesions within the D80 isodose line, and 1 patient of 6 had a lesion that crossed the D80 isodose line; 99% of the petient's pseudoprogression appeared inside the D80 isodose line. Planning data of the original tumors and the location of the recurrent tumors are shown in Figure 2.

Of the 9 who progressed while continuing TMZ treatment, 5 underwent surgery after TMZ, 4 received a combination of bevacizumab and irinotecan after TMZ, one had radiotherapy after TMZ; one had only combination of bevacizumab and irinotecan without receiving TMZ because of the adverse effects. The other 5 patients had only symptomatic treatment. Eight patients had pseudoprogression while continuing TMZ treatment and 5 had no progression in the follow-up period. The other 3 patients who had pseudoprogression progressed after a while; one had surgery after TMZ, one had surgery then a combination of

bevacizumab and irinotecan after TMZ, one had TMZ alone.

Survival analysis

The one- and and two-year survival of the thirty patients in this study were 89% and 37%, respectively, (median: 23 months, 95% confidence interval (CI): 19.8-26.1). In the last follow-up, 11 patients were alive (median: 27 months, range 8-42 months) and 19 patients had died of disease progression (median 20 months: range, 10-42 months). We had no record of death caused by adverse effects or other events.

The one- and two-year survival of the 14 patients who had central recurrence were 78% and 25% (median: 16 months, 95% CI: 7.5-24.4). The one- and and two-year survival of the 11 patients who had only in-field, marginal or distant recurrence were 100% and 40% (median: 24 months, 95 CI%: 22.5-25.5) (p= 0.01) (Figure 3). The one- and two-year survival of the 8 patients who had pseudoprogression were 83% and 62% (range, 9-34 months). There was no significant difference with the survival of patients who had no pseudoprogression (p= 0.37).

The one- and two-year PFS of the 14 patients who had central recurrence were 21% and 0% (median: 5 months, 95% CI: 3.2-6.8). The one- and two-year PFS of the 11 patients who had only in-field, marginal or distant recurrence were 36% and 27% (median: 11 months, 95% CI: 5.6-16.4) (p= 0.04) (Figure 4).

As a result, the location of recurrence was considered as a significant prognostic factor that affected both OS and the PFS.

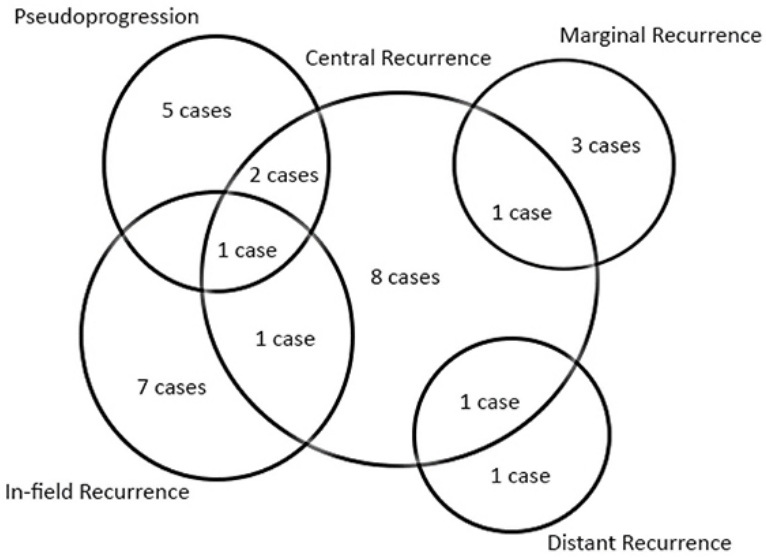

Figure 1: *Recurrence scheme of patients*

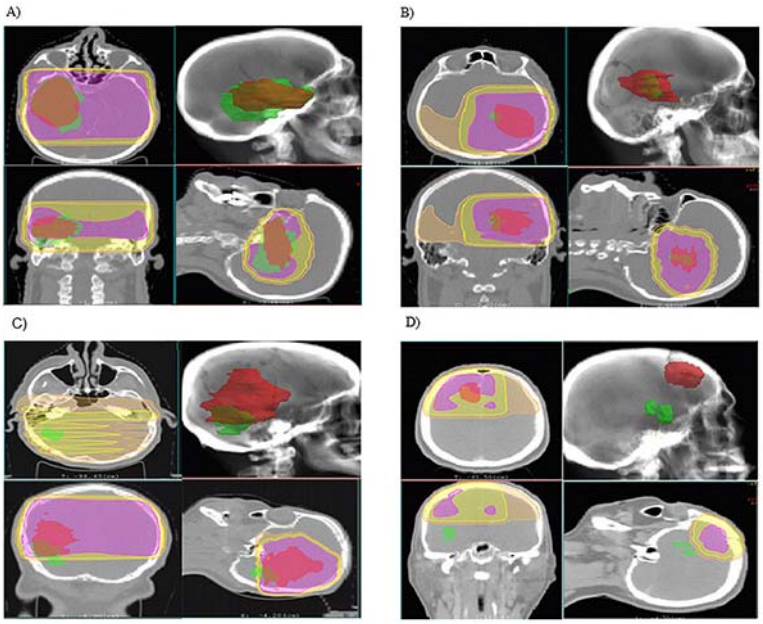

Figure 2: *The patients who had central (A), in-field (B), marginal (C), and distant (D) recurrences are shown respectively. The location of the primary tumor and the recurrent lesion considering isodose lines are viewed. Red: primary tumor, green: recurrent lesion, purple: D100 isodose line, yellow: D90 isodose line, orange: D80 isodose line.*

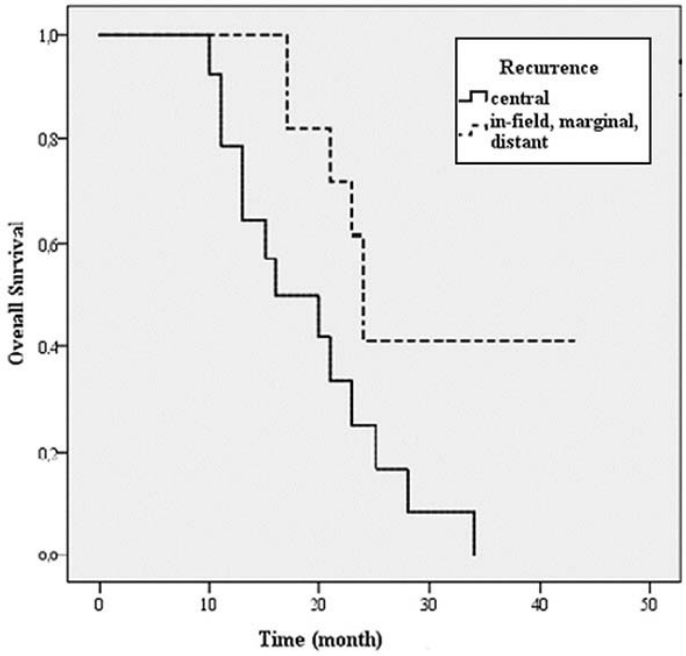

Figure 3: *Overall survival according to the locations of recurrence*

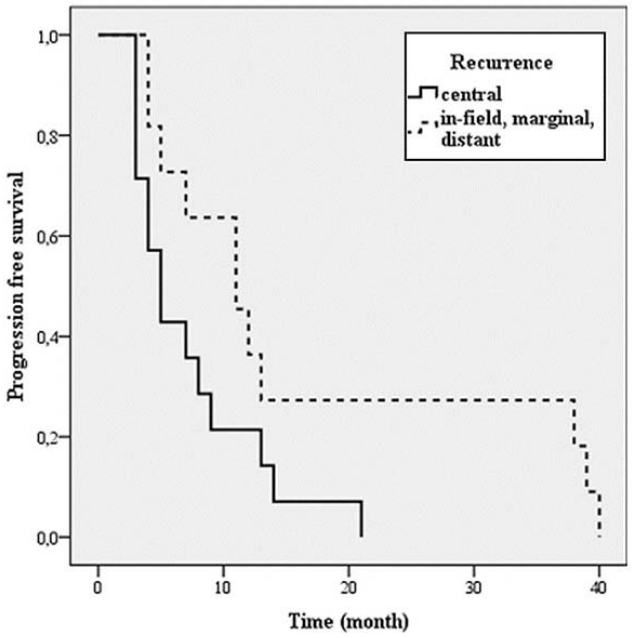

Figure 4: *Progression-free survival according to the locations of recurrence*

DISCUSSION

High-grade gliomas constitute 77% of malignant brain tumors, and GBM account for 82% of high-grade gliomas (6). In recent years, new treatment strategies have neither achieved progress in survival nor in disease control, and local recurrence remains the most significant problem.

The treatment of high-grade gliomas is postoperative chemoradiotherapy with TMZ and later with adjuvant TMZ. The changes of malignant glioma treatment introduced new problems in follow-up. First, for the standardization of processing recurrence, the Macdonald criteria were established (29). With the development of clinical practice, the Macdonald criteria were no longer satisfactory and were revised by the Neuro-Oncology Working Group and named the Response Assessment in Neuro-Oncology (RANO) criteria (25). These criteria have a significant role in the standardization of the definitions of high-grade glioma recurrence.

Only conventional MRI with contrast is mostly insufficient to distinguish between recurrence and radiotherapy changes. Diffusion MRI, perfusion MRI, MRI spectroscopy, and PET-CT are some of the screening techniques used to differentiate the two. For the true assessment of recurrence, improved screening techniques and more studies about radiologic follow-up and recurrence patterns need to be designed.

Our study researched the correlation between radiologic and clinical recurrence patterns after TMZ- based radiochemotherapy. The locations of recurrence, volumes, and the relation between the original tumor and time and size of recurrence was evaluated. The optimal definition of recurrence types, response and pseudoprogression were highlighted.

Owing to the limitations of the treatment response criteria of Macdonald et al., these criteria were revised an renamed the RANO criteria (24). According to the RANO criteria, when there is a contrast enhancing new lesion in the first 12 weeks after completing RT, progression can only be defined if the greater volume of that lesion is outside the 80% isodose line or confirmed as recurrence histopatologically. Otherwise, it is defined as pseudoprogression and adjuvant TMZ treatment is continued.

In the present study, 12 patients had progression with contrast MRI, diffusion MRI, perfusion MRI, and MRI spectroscopy in the first 12 weeks after completing RT. Eight (66.6%) of 12 patients had their recurrent lesion inside the 80% isodose line, 4 (33.3%) of 12 patients' recurrence crossed the 80% isodose line but the greater volume of their lesions were inside the 80% isodose line. In the follow-up period, these progressed lesions did not regress or lose contrast enhancement as would be expected of pseudoprogression.

In this study, 6 patients had pseudoprogression with contrast-enhanced MRI, diffusion MRI, perfusion MRI, and MRI spectroscopy in the first 12 weeks after completing RT. Five of 6 patients' lesions were inside the 80% isodose line, and one patients' lesion crossed the 80% isodose line. According to the RANO criteria, the lesion that crossed the 80% isodose line could be defined as progression, but by the following MRI, the lesion regressed and was radiologically proven as pseudoprogression. Accordingly, the RANO criteria has difficulties about differentiating progression and pseudoprogression.

In the Hochberg et al. study 42 patients with GBM treated with whole brain RT±chemotherapy were examined using CT in the 2nd month postmortem. Ninety percent of patients had recurrence 2 cm beyond the tumor region. With this study, consideration for local RT and higher target doses resulted (12). Garden et al. studied recurrence locations of 53 patients with high-grade gliomas who received local RT and 7 patients who had whole brain RT (39 had GBM and 21 had anaplastic astrocytoma). The mean tumor dose was 65.4 Gy. Thirty-five patients had BCNU±cisplatin chemotherapy. The one- and 2-year survival of the patients with GBM were 40% and 14%, respectively. The one- and 2-year survival of those with anaplastic astrocytoma were 76% and 52%, respectively. Thirty-four of 48 patients who had local RT had progression on follow-up CT. Six patients had new intracranial metastatic lesions, 3 of which were within the RT field and 3 were beyond the RT field. Twenty-one patients were reoperated at least once, 19 of whom were diagnosed as having recurrent tumor; 2 were histopathologically diagnosed as necrosis. According to their study, there was no difference in the survival of local RT and whole brain RT; new intracranial metastases appeared in the primary tumor field and did not affect survival (13).

Hess et al. studied 66 patients with malignant glioma who received RT alone using the multiple field technique. PTV was determined with a 2 cm margin as seen on preoperative CT and the total dose was 60 Gy. The median survival was 14 months and 86% of recurrences were within the treated volume. PTV and RT were used and considered appropriate for the radiotherapy of malignant glioma (16).

During research of the sufficiency of RT target volumes, Park et al. (2007) studied 23 patients with GBM for the first 4 postoperative weeks and then every 2 months post radiotherapy using MRI and MRI spectroscopy. In the follow-up period, 9 patients had new or increased contrast enhancement, and 14 patients had stable or decreased enhancement. Six patients who had a 2 or higher choline/N-acetyl aspartate (NAA) index in MRI spectroscopy and new or increased enhancement areas had their lesions completely in the 60 Gy isodose line, 3

patients who had a 2 or higher choline/N-acetyl aspartate (NAA) index had their lesions outside the 60 Gy isodose line. Eight (89%) of 9 patients's lesions that had new or increased contrast enhancement were closely beyond the primary tumor area. According to the study, the margins of RT target volumes were sufficient (18).

Brandes et al. studied 95 patients with GBM who received TMZ-based chemoradiotherapy followed by adjuvant TMZ. Methylation of methylguanine-methyltransferase (MGMT) and follow-up MRIs were evaluated. The median follow-up period was 18.9 months (range, 6.6-44.8 months). Seventy-nine (83%) patients had recurrence; 57 (72.2%) had in-field, 17 (21.5%) had distant, and 5 (6.3%) patients had marginal recurrence. The relation between methylation of MGMT and recurrence localization was assessed. Fifty-one (85%) patients who had in-field or marginal recurrence had unmethylated MGMT, and 11 (57.9%) had methylated MGMT (p=0.01). The recurrences outside the RT field appeared later than the in-field recurrences (14.9 vs 9.2 months, p=0.02) (19).

In the study of Milano et al. the MRIs before and after TMZ-based chemoradiotherapy of 54 patients with GBM were retrospectively evaluated. Central recurrence (local progression) and in-field, marginal and distant new lesions were assessed according to the 95% isodose line. Distant recurrence was defined as a new lesions appearing outside the 95% isodose line, in-field recurrence was defined as a new lesion appearing completely in the 95% isodose line, and marginal recurrence was defined as a new lesion crossing the 95% isodose line. In the median 17 months follow-up, 39 (72%) of 54 patients had recurrence; 80% had central recurrence (median 7 months after diagnosis), 33% had in-field recurrence (median 14 months), 15% had marginal recurrence (median 18 months), and 20% had distant recurrence (median 11 months). The one-year survival of central, in-field, marginal, distant, and of any recurrence were 46%, 15%, 3%, 14%, and 25%, respectively. The two-year survival of central, in-field, marginal, distant and of any recurrence were 68%, 60%, 32%, 28%, and 66%, respectively (28).

In our study, similiar to the latest studies, central and in-field recurrence were seen more often than marginal and distant recurrence. The survival of new in-field, marginal and distant recurrence was longer and these new lesions developed later than central recurrences. Additional new studies need to be organized about the standardization of treatment response, radiologic screening techniques need to be improved and more effective treatment options need to be experienced.

CONCLUSION

This study researched the clinical and radiologic behavior of recurrence after radiochemotherapy in patients with high-grade glioma and concluded that the overall survival and the progression-free survival of central recurrence was shorter than new in-field, marginal, and distant recurrence. Central recurrence is thought to be a negative prognostic factor. Improved radiologic modalities such as diffusion MRI, perfusion MRI, and MRI spectroscopy help to differentiate recurrences through changes after radiochemotherapy.

For the better management of high-grade gliomas, it is important to determine the biologic characteristics of recurrence. New studies should aim to identify recurrence patterns, response to treatment, and determine prognostic factors.

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Correspondence to:
Serra Kamer
E-mail: serra.kamer@gmail.com

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REFERENCES

1. *Mehta MP. Overview, Central Nervous System Tumors. In: Gunderson LL, Tepper JE, ed. Clinical Radiation Oncology Third Edition. Philadelphia: Elsevier Saunders; 2012: 441-442.*
2. *CBTRUS: Central Brain Tumor registry of the United States Statistical Report: Primary Brain Tumors in the United States, 1997-2001. Hindsdale, IL, CBTRUS,2004.*
3. *Mirimanoff RO, Gorlia T, Mason W, et al. Radiotherapy and temozolomide for newly diagnosed glioblastoma: recursive partitioning analysis of the EORTC 26981/22981-NCIC CE3 phase III randomized trial. J Clin Oncol 2006;24:2563-2569.*
4. *Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-996.*
5. *Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomized phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009;10:459-466.*
6. *Brandes A, Tosoni A, Franceschi E, et al. Pseudoprogression after concomitant radio-chemotherapy treatment in newly diagnosed glioblastoma patients and potential correlation with MGMT methylation status. Neuro-Oncology, USA: Duke Univ Press; 2007; 9: 529.*
7. *Chaskis C, Neyns B, Michotte A, De Ridder M, Everaert H. Pseudoprogression afterradiotherapy with concurrent temozolomidefor high-grade glioma: Clinical observations and working recommendations. Surg Neurol 2009;72:423-428.*
8. *Chamberlain MC, Glantz MJ, Chalmers L, Van Horn A, Sloan AE. Early necrosis following concurrent Temodar and radiotherapy in patients with glioblastoma. J Neurooncol 2007;82:81-83.*
9. *Cross NE, Glantz MJ. Neurologic complications of radiation therapy. Neurol Clin 2003;21: 249-277.*
10. *Taal W, Brandsma D, de Bruin HG, et al. Incidence of early pseudoprogression in a cohort of malignant glioma patients treated with chemoirradiation with temozolomide. Cancer 2008;113:405-410.*
11. *Gaspar LE, Fisher BJ, MacDonald DR, et al. Supratentorial malignant glioma: Patterns of recurrence and implications for external beam local treatment. Int J Radiat Oncol Biol Phys 1992;24:55-57.*
12. *Hochberg FH, Pruitt A. Assumptions in the radiotherapy of glioblastoma. Neurology 1980;30:907-911.*
13. *Garden AS, Maor MH, Yung WK, et al. Outcome and patterns of failure following limited-volume irradiation for malignant astrocytomas. Radiother Oncol 1991;20:99-110.*
14. *Wallner KE, Galicich JH, Krol G, Arbit E, Malkin MG. Patterns of failure following treatment for glioblastoma multiforme and anaplastic astrocytoma. Int J Radiat Oncol Biol Phys 1989;16:1405-1409.*
15. *Gaspar LE, Fisher BJ, Macdonald DR, et al. Supratentorial malignant glioma: Patterns of recurrence and implications for external beam local treatment. Int J Radiat Oncol Biol Phys 1992;24:55-57.*
16. *Hess CF, Schaaf JC, Kortmann RD, Schabet M, Bamberg M. Malignant glioma: Patterns of failure following individually tailored limited volume irradiation. Radiother Oncol 1994;30:146-149.*
17. *Aydin H, Sillenberg I, von Lieven H. Patterns of failure following CT-based 3-D irradiation for malignant glioma. Strahlenther Oncol 2001;177:424-431.*
18. *Park I, Tamai G, Lee MC, et al. Patterns of recurrence analysis in newly diagnosed glioblastoma multiforme after three-dimensional conformal radiation therapy with respect to pre-radiation therapy magnetic resonance spectroscopic findings. Int J Radiat Oncol Biol Phys 2007;69:381-389.*
19. *Brandes AA, Tosoni A, Franceschi E, et al. Recurrence pattern after temozolomide concomitant with and adjuvant to radiotherapy in newly diagnosed patients with glioblastoma: Correlation with MGMT promoter methylation status. J Clin Oncol 2009;27:1275-1279.*
20. *Walker MD, Strike TA, Sheline GE. An analysis of dose-effect relationship in the radiotherapy of malignant gliomas. Int J Radiat Oncol Biol Phys 1979;5:1725-1731.*

21. *Bleehen NM, Stenning SP. A Medical Research Council trial of two radiotherapy doses in the treatment of grades 3 and 4 astrocytoma. The Medical Research Council Brain Tumour Working Party. Br J Cancer 1991;64:769-774.*
22. *Nakagawa K, Aoki Y, Fujimaki T, et al. High-dose conformal radiotherapy influenced the pattern of failure but did not improve survival in glioblastoma multiforme. Int J Radiat Oncol Biol Phys 1998;40:1141-1149.*
23. *Fitzek MM, Thornton AF, Rabinov JD, et al. Accelerated fractionated proton/photon irradiation to 90 cobalt gray equivalent for glioblastoma multiforme: Results of a phase II prospective trial. J Neurosurg 1999;91:251-260.*
24. *Mehta MP, Masciopinto J, Rozental J, et al. Stereotactic radiosurgery for glioblastoma multiforme: Report of a prospective study evaluating prognostic factors and analyzing long-term survival advantage. Int J Radiat Oncol Biol Phys 1994;30:541-549.*
25. *Wen PY, Macdonald DR, Reardon DA, Cloughesy TF et al. Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group J Clin Oncol 2010; 28: 1963-1972.*
26. *d de Wit MC, de Bruin HG, Eijkenboom W, Sillevis Smitt PA, van den Bent MJ. Immediate post-radiotherapy changes in malignant glioma can mimic tumor progression. Neurology 2004; 63:535-537.*
27. *Brandsma D, Stalpers L, Taal W, Sminia P, van den Bent MJ. Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas. Lancet Oncol 2008; 9:453-461.*
28. *Milano Michael T, Okunieff P, Donatello R,et al. Patterns and timing of recurrence after temozolomide-based chemoradiation for glioblastoma. Int J Radiat Oncol Biol Phys. 2009; 78: 1147-1155.*
29. *Macdonald DR, Cascino TL, Schold SC Jr, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol. 1990; 8: 1277-1280.*