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Distinction of Pseudoprogression in Glioblastoma Multiforme After Treatment: Utility of Ratio of Decrease in rCBV and rCBF on Serial Perfusion Magnetic Resonance Imagings

Glioblastoma Multiforme'de Tedavi Sonrası Psödoprogresyonun Ayrımı: Seri Perfüzyon Manyetik Rezonans Görüntülemede rCBV ve rCBF Azalma Oranının Yararı

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Abstract

Aim: To assess the value of perfusion magnetic resonance imaging (pMRI) in the differentiation of early pseudoprogression from true progression in glioblastoma multiforme (GBM) patients taking Temozolomide (TMZ) with radiotherapy (RT) treatment.

Materials and Methods: Pre-RT and post-RT cranial pMRI scans of 23 GBM patients treated with RT-TMZ were reviewed. Relative cerebral blood volume (rCBV) and relative cerebral blood flow (rCBF) of the residual enhancing lesions were measured on serial pMRI scans and proportioned. Receiver operating characteristic (ROC) analysis was performed to determine a threshold ratio of the decrease in rCBV and rCBF.

Results: There were nine patients (39%) with signs of radiological progression, of whom six (67%) had real progression and three (33%) had pseudoprogression based on follow-up MRI studies, clinical parameters, and/or pathology. The ratio of decrease was 2.928 in rCBV and 2.510 in rCBF in the pseudoprogression group, which were significant according to Mann-Whitney *U* test (p=0.02). Cut-off ratio of decrease value of 1.73 for rCBV and 1.62 for rCBF between pre-RT and post-RT pMRI studies, could differentiate the presence of early pseudoprogression with 100% sensitivity and 100% specificity.

Conclusion: The ratio of decrease in rCBV and rCBF is a reliable predictor of early pseudoprogression in GBM patients under RT-TMZ treatment.

Keywords: Perfusion; magnetic resonance imaging; glioblastoma multiforme; pseudoprogression; radiotherapy

Öz

Amaç: Radyoterapi (RT) ve Temozolomid (TMZ) tedavisi alan glioblastoma multiforme (GBM) hastalarında erken psödoprogresyonun gerçek progresyondan ayrımında perfüzyon manyetik rezonans görüntülemenin (pMRG) değerinin değerlendirilmesi.

Gereç ve Yöntemler: Radyoterapi ve Temozolomid tedavisi alan ve RT öncesi ve sonrası kranial pMRG tetkikleri olan 23 hasta değerlendirildi. Rölatif serebral kan hacmi (rCBV) ve rölatif serebral kan akımı (rCBF), seri MRG tetkikleri ile değerlendirilerek oranlandı. rCBV ve rCBF değerlerinde azalma oranı eşik değerinin belirlenmesi için receiver operating characteristic (ROC) analizi uygulandı.

Bulgular: Dokuz (%39) hastada radyolojik progresyon bulguları saptandı. Bu hastalar takip MRG tetkikleri, klinik parametreler ve/veya patolojik bulgular ile birlikte değerlendirildiğinde altısı (%67) gerçek progresyon iken, üçü (%33) psödoprogresyon olarak saptandı. Psödoprogresyon grubunda rCBV ve rCBF azalma oranları sırasıyla 2.928 ve 2.510 olup Mann-Whitney *U* testine göre fark anlamlı idi (p=0.02). RT öncesi ve sonrası pMRG tetkiklerinde saptanan rCBV ve rCBF azalma oranı eşik değerleri (sırasıyla 1.73 ve 1.62) erken psödoprogresyonu ayırt etmede %100 duyarlı ve %100 özgül olarak bulundu.

Sonuç: Radyoterapi ve Temozolomid tedavisi alan GBM hastalarında rCBV ve rCBF azalma oranı erken psödoprogresyonun güvenilir bir göstergesidir.

Anahtar Sözcükler: Perfüzyon; manyetik rezonans görüntüleme; glioblastoma multiforme; psödoprogresyon; radyoterapi

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Introduction

Glioblastoma multiforme (GBM) is the most common malignant brain neoplasm in adults. It accounts for 12-15% of all intracranial tumors and 50-60% of astrocytic tumors (1). In 1980s, studies about treatment revealed that RT after resection has a better outcome with respect to surgery alone, and postoperative RT has become the current standard of care (2). Despite improvements in treatment modalities, treatment results did not change much. Therefore, studies on different chemotherapeutics became prevalent to increase overall survival. Temozolomide (TMZ) is one of the oral alkylating agents which methylates the DNA of tumor cells, damages and triggers the death of tumor cells in brain neoplasms (3). After studies of European Organization for Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada (NCIC), adjuvant and concomitant TMZ with RT after resection has become the standard treatment regimen in which an additive growth inhibition is achieved (4).

In brain neoplasms, the blood brain barrier (BBB) is usually disrupted due to tumoral and endothelial cell death after effective treatments such as RT and concomitant TMZ. Therefore, treated lesions might seem larger in magnetic resonance imaging (MRI) even one month after chemotherapy since gadolinium passes from BBB (5). This phenomenon, which may mimic tumor growth, is called as pseudoprogression (6).

Magnetic resonance imaging is widely used in the diagnosis of brain neoplasia and evaluation of tumor response after therapy. Gadolinium-derived contrast agents have contribution in assessment of residual tumor and post therapeutic changes, but they still have some limitations. New functional magnetic resonance imaging techniques establish correct tumor staging and help in treatment planning (7). Among those techniques, perfusion MRI (pMRI) has an important role in assessment of response since it determines tissue blood flow dynamics (8,9). The purpose of the present study was to assess the value of pMRI in the differentiation of early pseudoprogression from true progression in GBM patients under RT-TMZ treatment by comparing pre-RT and post-RT pMRI studies.

MATERIALS AND METHODS

Patient Selection

Patients who took diagnosis of GBM and had adjuvant and concomitant TMZ with RT after the operation were reviewed. Institutional review board approval was obtained (approval number: 2022/06-27). Inclusion criteria required (i) a diagnosis of GBM and (ii) contrast-enhanced MRI and pMRI studies before RT and in the first and fourth months after RT on a 1.5 T MRI unit in the same institution. Therefore, every patient would have three MRI studies after operation.

In a period of one year, 44 patients had a diagnosis of GBM. After excluding 17 patients with MRI studies in different institutions and four died in the postoperative period, 23 patients (15 men, eight women; age range, 29-74 y; mean age, 53 y) were included in the study. Cranial MRI studies of those patients were evaluated retrospectively from electronic archive system.

MRI Technique

All patients included in the study had contrast-enhanced cranial MRI and pMRI in a 1.5 Tesla MR scanner (Magnetom Symphony Vision; Siemens, Erlangen, Germany). MR imaging protocol included axial turbo spin-echo T2-weighted sequence, 3 natural orthogonal planes pre-contrast T1-weighted sequence and coronal fluid attenuated inversion recovery sequence. Gradient-echo echo-planar imaging T2-weighted dynamic susceptibility contrast sequence with gadopentate dimeglumine (Gd-DTPA) given as a bolus at a dose of 0.1 mmol/kg via 20-ga canula from antecubital fossa by using a power injector at a rate of 3mL/s. 20 ml saline injection was applied after contrast. Three orthogonal planes T1-weighted sequences were taken after contrast administration.

Image analysis

Localization and dimensions of the residual enhancing lesions were evaluated. In the axial plane with largest dimension of residual lesion, two perpendicular diameters were measured and products of them were recorded in serial MRI studies. Response was defined according to updated RANO (Response-Assessment in Neuro-Oncology Working Group) criteria (10) in conjunction with clinical evaluation and dexamethasone dose, and classified into four grades as complete response, partial response, stable disease, and progression. Pseudoprogression was defined as absence of tumor progression at a second reoperation, or no further progression or spontaneous improvement on subsequent MRI without new anti-tumor therapy nor increase in dexamethasone dose (6). Among the patients in the progression group, patients having an increase in residual tumor dimension in follow-up MRIs were defined as true progression and patients with a decrease in tumor dimension or stable tumor dimension were set to pseudoprogression group. One patient in the progression group with reoperation after post-RT MRI, who took histopathological diagnosis of radiation-induced changes, was also included into pseudoprogression group.

Dynamic contrast-enhanced MRIs were evaluated on a post-processing workstation (Leonardo Workstation; Siemens Medical Solutions, Forcheim, Germany) by two radiologists with consensus and tumor response was confirmed with subsequent follow-up MRIs, which were repeated every three months. Region of interest (ROI) with a standard size (0.16 cm^2) was placed over the mostly enhanced area of the residual tumor and normal contralateral white matter. Mean rCBV and rCBF values were calculated after three measurements for each area in every MRI study.

Statistical analysis

Statistical analysis was performed with SPSS software (version 15.0; IBM, Armonk, New York). rCBV and rCBF values of the residual lesions before and after RT were

proportioned and difference between true progression and pseudoprogression group was evaluated by Mann-Whitney *U* test. Receiver operating characteristic (ROC) analysis was performed to determine threshold ratio of decrease in rCBV and rCBF values to differentiate pseudoprogression from true progression. Differences were considered significant when *p* values were less than 0.05.

RESULTS

Final study cohort included 23 patients who met inclusion criteria. For the evaluation of residual tumor, first MRI study was applied before RT-TMZ treatment. Mean duration between first MRI in the postoperative period and RT was 13 days. Demographic characteristics of the patients, location of the residual lesions and response to treatment in the follow–up MRI are reviewed in Table 1.

Among 23 patients, nine of them showed progression radiologically after RT-TMZ treatment. But three of those nine patients were grouped as pseudoprogression in the follow- up (Fig. 1). Only one patient was taken to operation due to clinical deterioration and radiological progression and was diagnosed as radiation-induced changes and pseudoprogression pathologically. Patients in the pseudoprogression group constituted 13% of all patients and 33% of the patients in the progression group. Incidence of progression in the first MRI study after RT-TMZ treatment was 39% and incidence of true progression in the follow-up was 26%.

rCBV values after RT-TMZ treatment in the true progression group varied between 3.5 and 8.4 (mean 6.5). rCBV values of the three cases in the pseudoprogression group were 2.6, 1.9 and 1.6. When first MRI study after the operation and MRI study one month after RT-TMZ treatment compared, ratio of decrease was 2.928 ± 0.616 in rCBV ($rCBV_{pretreatment}/rCBV_{intertreatment}$) and 2.510 ± 0.305 in rCBF ($rCBF_{pretreatment}/rCBF_{intertreatment}$) in the pseudoprogression group (Table 2). Decrease in rCBV and rCBF ratios were significant according to Mann-Whitney *U* test (*P*= .02). In the progression group, similar to the pseudoprogression group, the ratio of rCBVs and ratio of rCBFs were also statistically significant (*P*= .02). Ratio of rCBVs was 0.999± 0.036 and ratio of rCBF was 1.059 ± 0.077 (Table 3). Cut-off ratio value of 1.73 for rCBV and 1.62 for rCBF between pre-RT and post-RT pMRI study, was found to differentiate two entities with 100% sensitivity and 100% specificity for the presence of tumor pseudoprogression according to the results of ROC analysis (Figs 2 and 3).

DISCUSSION

The combination of TMZ with RT caused a great advance in treatment of patients with GBM (4). This treatment regimen was demonstrated to increase overall survival when compared to RT alone in several studies with large series (4, 11). After the studies of European Organization for Research and Treatment of Cancer, and National Institute of Canada; postoperative RT and concomitant TMZ (75mg/m^2/day for 6 weeks) followed by six months of adjuvant TMZ (150-200mg/m^2/d for five days every 28 days) has become the current standard treatment in GBM (4).

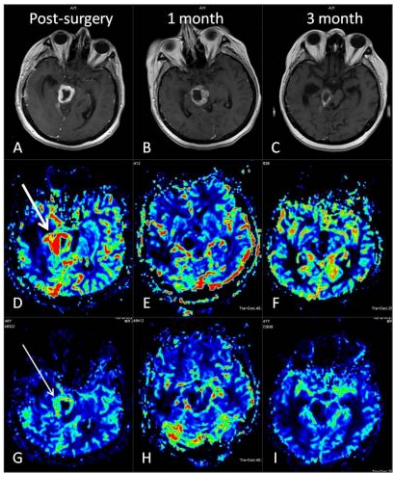
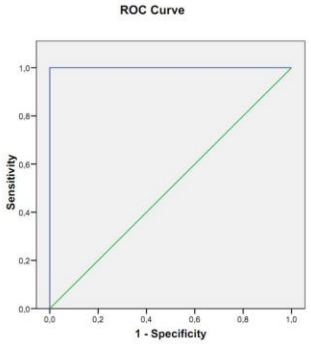
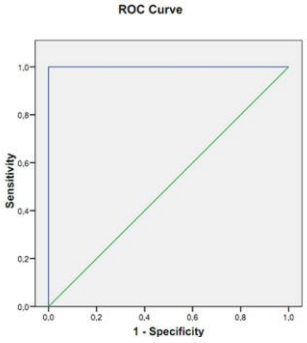


Fig 1. Pseudoprogression of the residual tumor in a 41 year-old woman with GBM. **A:** Axial T1-weighted image after the operation shows contrast enhancement in the walls of postoperative cavity at right side of mesencephalone. **B:** One month after RT-TMZ, cavitary lesion gets bigger and contrast enhancement becomes nodular. **C:** Lesion gets smaller and contrast enhancement decrease in the 3. month MRI study. **D-F:** rCBV maps in serial MRI studies demonstrate that cavitary lesion has increased perfusion after operation (d, thick arrows) but perfusion decrease in subsequent MRI studies one month (e) and three month (f) after RT-TMZ treatment. **G-I:** rCBF maps in serial MRI studies demonstrate similar findings as rCBV map. Blood flow of the lesion is high before RT (g, thin arrow) but in first month MRI, flow decrease although dimensions increase (h). Three months after RT-TMZ flow on the walls of the lesion is not remarkable (i).



Positive if Less Than or Equal To[a]	Sensitivity	1 - Specificity
-,04762	,000	,000
,96414	,167	,000
,98060	,333	,000
,99265	,500	,000
1,01429	,667	,000
1,04026	,833	,000
1,73650	1,000	,000
2,58553	1,000	,333
3,18269	1,000	,667
4,61538	1,000	1,000

Fig 2. Receiver operating characteristic (ROC) analysis for differentiation of progression and pseudoprogression with decrease ratio of rCBV values between follow-up MRI studies.



Positive if Less Than or Equal To[a]	Sensitivity	1 - Specificity
-,07955	,000	,000
,93047	,167	,000
,98923	,333	,000
1,05953	,500	,000
1,08402	,667	,000
1,08963	,833	,000
1,62510	1,000	,000
2,41228	1,000	,333
2,68627	1,000	,667
3,70588	1,000	1,000

Fig 3. Receiver operating characteristic (ROC) analysis for differentiation of progression and pseudoprogression with decrease ratio of rCBF values between follow-up MRI studies.

Table 1. Patient details, tumor locations and treatment response

PATIENTS					TREATMENT RESPONSE			
No	Age	Sex	Tumor location		Post RT-TMZ	3.mo	6.mo	9.mo
1	41	F	Brain stem-thalamus		PD	PR		
2	29	F	Cerebellum		PD	PR		
3	67	M	Temporoparietal		PD	SO		
4	59	F	Temporoparietal		PD	PD		
5	57	M	Temporoparietal		PD	PD		
6	42	M	Temporal		PD	PD		
7	56	M	Temporoparietal		PD	PD		
8	58	M	Biparietal		PD	PD		
9	38	F	Temporoparietal		PD	PD	PD	
10	59	F	Occipital		TR	TR	TR	
11	56	M	Temporoparietal		PR	SD		
12	53	M	Temporal		PR	SD		
13	38	M	Frontotemporal		SD	SD	SD	SD
14	45	M	Frontoparietal		PR	PR	TR	TR
15	45	M	Frontal		PD	TR		
16	49	M	Temporal		SD	SD		
17	59	F	Frontal		PR	TR		
18	73	M	Parietooccipitotemporal		PR	SD		
19	57	M	Temporal		PR	SD		
20	55	M	Parietal		SD	SD	PR	TR
21	52	M	Parietal		SD	SD	PR	
22	63	F	Frontal		PR	PR	SD	
23	74	F	Temporal		PR	SD	SD	

PD, progressive disease; PR, partial response; SD, stabile disease; TR, total response; SO, second operation; M, male; F, female; TMZ,Temozolomide; RT,radiotherapy

Table 2. Ratio of decrease in rCBV and rCBF values in the pseudoprogression group

	Mean ± SD	Maximum	Minimum	Median
rCBV	2.928 ± 0.616	3.615	2.421	2.750
rCBF	2.510 ± 0.305	2.706	2.158	2.666

rCBV, relative cerebral blood volume; rCBF, relative cerebral blood flow

Table 3. Ratio of decrease in rCBV and rCBF values in the progression group

	Mean ± SD	Maximum	Minimum	Median
rCBV	0.999 ± 0.036	1.052	0.952	0.992
rCBF	1.059 ± 0.077	1.092	0.920	1.026

rCBV, relative cerebral blood volume; rCBF, relative cerebral blood flow

However, with the realization that some patients with radiological worsening or clinical deterioration following the completion of chemoradiation are not true progression pathologically, reports on the issue of pseudoprogression have increased. In clinical practice, patients with radiological and clinical progression are usually taken into reoperation or biopsy with recurrent tumor suspicion. This may lead to unnecessary interventions and interruption of TMZ treatment in cases with pseudoprogression, who would have maximum benefits from TMZ (12). Therefore, tumor response assessment and distinction of true vs. pseudoprogression in this context, is important,

particularly in the early period before the initiation of a second intervention.

In daily practice, contrast-enhanced MRI is the first choice in the evaluation of treatment response after chemoradiation (13). However, MRI findings are not always easy to evaluate in those cases. In the postoperative assessment, after the second day, there is usually linear contrast enhancement in the operation borders. After one week, enhancement may become thicker and nodular, presumably from postoperative subacute ischemic changes, making the distinction of granulation tissue and residual tumor difficult (1). Major difficulty after RT is to differentiate residual or recurrent tumor from radiation necrosis on imaging. A ring enhancing mass with variable edema and a mass effect may be radiological findings of radiation-induced brain damage (14). Thus, contrast enhancement due to an increased blood-brain barrier is nonspecific in those cases (15). Some factors, such as total radiation dose, total time of dose, dose in each RT frame, number of RT frames and age of the patient, effect development of radiation necrosis (16). Influence of the RT may be seen in the early (in the first weeks) or late (after four weeks to years) period. Signs and symptoms of radiation necrosis are usually nonspecific and the best way for the prompt diagnosis is follow-up MRI studies (1).

After an effective treatment such as RT and adjuvant TMZ, due to endothelial and tumoral cell death, the BBB is usually destroyed, and permeability is increased even within one month after chemotherapy. Due to gadolinium passage from destroyed BBB, lesions may seem larger on MRI when compared to pre-RT MRI scans (5). This condition may be interpreted inadvertently as tumor enlargement (13). In the follow-up MRIs of patients with initial progression, when the lesions stayed stable or regressed and the term “pseudoprogression” was given to that phenomenon (6). The reason of the pseudoprogression is still not well understood, but the most likely mechanism is that RT-TMZ treatment causes more tumoral and endothelial cell death in comparison to RT alone (6, 17-18). Cell death causes vasodilatation, peritumoral edema, and abnormal increase in vascular permeability with disruption in the BBB which mimics real progression in enhancing areas (6, 19). In the literature, pseudoprogression rates varied from 12% to 64% of the progression group (17-21). Results of our study were compatible with those studies as we diagnosed 33% of the progressing cases as pseudoprogression. To minimize the likelihood of overestimating the benefits of treatment, Clarke et al. (22) proposed to consider findings on the post-RT MRI as a new baseline because of high risk of pseudoprogression. However, this may be misleading in our opinion, due to the possibility of a delay for a necessary intervention in real tumor progression. Therefore, a reliable method should be developed for distinguishing true progression from early pseudoprogression.

Response assessment is a developing scope of advanced MRI techniques. There are several reports which exhibit the role of perfusion MRI in the response assessment of RT-TMZ treatment (23, 24). Before standard use of RT-TMZ, Sugahara et al. studied rCBV ratios in pMRI of 20 GBM patients after RT (8). They showed rCBV was greater than 2.6 in recurrent tumor and less than 0.6 in normal parenchyma. According to study of Bobek-Billewicz et al., rCBV was greater than 1.7 in recurrent tumor and less than 1.0 in post therapeutic changes (25). Different cut–off values of rCBV are reported in different studies between 1.47 and 2.12 to detect pseudoprogression (26-28). In the present study, rCBV values of three cases with pseudoprogression after RT-TMZ treatment were measured as 2.6, 1.9 and 1.6, respectively, which were relatively high compared to literature. According to our results, rCBV values were not able to differentiate real progression from pseudoprogression alone. This may depend on several reasons. For instance, in the setting of high capillary permeability with substantial contrast material leakage, a potential pitfall of rCBV maps derived from dynamic susceptibility-weighted contrast-enhanced MR imaging occurs. When the rate of leakage is high, rCBV values may be underestimated (29). On the other hand, type of the contrast agent used in pMRI may also affect rCBV values (30).

To distinguish pseudoprogression from true progression, Tsien et al. used a parametric response map (PRM) for quantifying therapy-associated hemodynamic alteration with the hypothesis that a voxel-based approach may be more sensitive than mean tumor average of rCBV (31). PRM map was determined by calculating the difference between serial rCBV maps (i.e., intertreatment-pretreatment) for each voxel. They proposed that PRM was a potential early imaging biomarker of response. Boxerman et al. reported that both absolute and percentage changes from the initial progressive enhancement to first subsequent follow-up were significantly different between pseudoprogression and progressive disease (32). Instead of using difference, we used ratios of decrease (i.e., pretreatment /intertreatment) in rCBV and rCBF values as early imaging parameters of response to have more reliable results. Ratio seems to individualize the parameters to for each tumor and hence could be a better measure to assess progression status. In our opinion, ratio could offset technical hurdles which derives from estimation of rCBV. When pMRIs before RT and one month after RT-TMZ treatment were compared, in radiologically progressed cases, more than 1.73 times decrease in rCBV ratio, and more than 1.62 times decrease in rCBF ratio differentiated pseudoprogression with 100% sensitivity and 100% specificity.

This study has several limitations. First, the results reported in the present study are based on observations made in a relatively small number of patients, causing a major limitation of the study. Therefore, the statistical power of the study and how far the cut-off remains valid need to be proven in larger series. However, we studied on a very specific patient group and tried to generate a hypothesis using an advanced MRI technique. Second, it

was a single- center study leading to limited interpretation of the results. Third, differences in pMRI technique or variable permeability of the vasculature among patients may have influenced rCBV in the pseudoprogression group, resulting in relatively high values, which was inevitable in this study.

In conclusion, the results of the present study point to the potential value of assessment of perfusion MRI parameters temporally in differentiating pseudoprogression from true progression in GBM patients. By using the ratio of decrease in rCBVs and rCBFs among serial pMRIs, pseudoprogression could be diagnosed in the early period, secondary operations could be avoided, and TMZ therapy could be continued. Verification of these results in larger studies is warranted.

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OŞ, HŞ, MCÇ: Conception and and design, OŞ: Acquisition of data, OŞ, HŞ, MCÇ: Analysis and interpretation of data, OŞ, HŞ: Reviewing the literature, drafting the article and writing, MCÇ: Study supervision, critically revising the article.

All authors took part in the study design and approve the final version of the manuscript.

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