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Radiotherapy in the Treatment of Low-Grade Gliomas

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Abstract

Objective: In the current classification of brain tumors of the World Health Organization, various tumor histologies have been categorized under the main heading of glial tumors. The subgroup of low-grade gliomas comprises grade 2 diffuse astrocytic and oligodendroglial tumors.

Methods: The primary treatment of low-grade gliomas is surgery. Safe maximal resection is the widest possible resection without causing additional neurological damage. It increases survival and reduces existing neurological symptoms. Maximal safe resection may not be achieved because of tumor infiltration or proximity to sensitive motor/sensory function areas. Although radio diagnostic and surgical technique advancements have improved, residual tumors are detected in the majority of patients.

Results: Adjuvant treatment of residual low-grade gliomas is controversial. The European Organisation for Research and Treatment of Cancer (EORTC) study showed that early radiotherapy after surgery extended progression-free survival for 2 years without an overall survival benefit. After this study, it has been adopted in clinical practice that high-risk patients receive early radiotherapy and low-risk groups receive radiotherapy after progression. Certain risk factors have been determined from Radiation Therapy Oncology Group (RTOG) and EORTC studies. The high-risk factors are age over 40 years, partial resection, tumor size over 5 cm, not having isocitrate dehydrogenase mutation, and tumor progression or recurrence. Adjuvant radiotherapy and concurrent chemotherapy are recommended achieving improved progression-free survival and overall survival in patients with high-risk factors. In the low-risk group, radiotherapy may be delayed until progression.

Conclusions: Low-grade gliomas are slow progressing tumors. To detect progression in follow-up, it is recommended to compare follow-up magnetic resonance images with the initial reference magnetic resonance images, not with the previous control.

Keywords: Low Grade Glial tumors, Radiotherapy, Chemotherapy, Side effects of RT

In the current classification of brain tumors of the World Health Organization (WHO), various histological subtypes have been categorized under the main heading of glial tumors. The subgroup of adult type diffuse gliomas is defined as astrocytoma (isocitrate dehydrogenase (IDH) mutant) and oligodendroglioma (IDH mutant and 1p19q co-deleted). In clinical practice, grade 2 oligodendrogliomas and astrocytomas are referred as low-grade gliomas. In the recent histological and molecular-integrated classification system, grade 2 tumors are grouped according to IDH mutant and 1p19q co-deletion.[1]

The natural history of low-grade gliomas is well recognized with its slow but sometimes unpredictable progression rate. It is also well documented that these tumors may dedifferentiate and progress as high-grade tumors. The gold standard radiological method is cranial magnetic resonance imaging (MRI). Increased signals in T2 and T2 FLAIR are sequences of MRI are used in diagnosis and follow-up.[2-4]

Surgery is the mainstay treatment for LGG. The main aim of surgery is to remove as much as a tumor without harming the patient and to obtain tumor tissue for pathological assessment. Novel techniques such as functional MRI, tractography, neuromonitorization, intraoperative MRI, awake craniotomy, etc. are used to increase the amount of resection without neurological damage.[5] Despite all these developments, the residual tumor is still detected in many patients after surgical removal. Shaw et al[6] examined the postoperative MRIs of 111 patients from the low-risk arm of RTOG 9802 study, who were reported to have undergone safe maximal resection according to the surgery note/surgeon's opinion. Residual tumors were detected to be <1 cm in 59%, 1-2 cm in 32%, and >2 cm in 9%.[6]

The effectiveness of radiotherapy (RT) after total or subtotal resection has been the subject of debate for many years. In the 1980s, 2 main randomized studies were conducted to test RT effectiveness; studies of "Believers" and "Non-Believers."

Effectiveness of RT

The effectiveness of RT was investigated in the EORTC 22845, "Non-Believers" trial. In this study, 311 patients were randomized to early RT (within 2 months) and follow-up arms. The 5-year progression-free survival (PFS) increased in the RT arm. However, no difference in overall survival (OS) was observed. While the median time to progression was 5.4 years in the RT arm, it was 3.7 years in the control group. It was observed that seizures were better controlled in the RT arm at 1 year (P = .0329). Also, it was shown that RT did not increase tumor dedifferentiation in patients who were operated on after progression. Survival after progression was 3.4 years for the control group and 1 year for the RT group (P < .0001).[7] It can be argued that the administration of radiotherapy to 65% of the progressed patients in the control group contributes to OS. Although this study demonstrates the effectiveness of RT, whether RT should be performed in the early postoperative period or after progression is still unknown. In this situation, selecting patients with good

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prognostic features and delaying RT in this group may be beneficial to postpone RT radiation-induced neurocognitive deterioration. Therefore, risk groups were evaluated in the EORTC studies in the "Believers" and "Non-believers" trials examining the radiotherapy dose. Since delayed RT does not adversely affect survival in some patients, it is important to identify which patients will progress early or late.

RT Dose

Radiotherapy dose in LGGs was evaluated in 2 randomized studies. The EORTC "Believers" trial compared 45 Gy-59.4 Gy, whereas the North American Intergroup study compared 50.4 Gy-64.8 Gy.[8,9] It was observed that increasing the dose did not affect PFS and OS. In addition to these studies, 54 Gy, which was used in the EORTC "Non-Believers" trial and whose effectiveness has been proven, is found to be between the standard dose range of 45 Gy-54 Gy. The dose is determined according to the treatment volume.[10] In the study of Shaw et al[9] comparing NCCTG/RTOG 50.4 Gy and 64.8 Gy, it was shown that high-dose RT did not increase PFS but increased the risk of radiation necrosis.[9] In current studies, 50.4 Gy is preferred as the standard dose.

Risk Groups

According to the EORTC 22844 and EORTC 22845 studies, age over 40 years, tumors larger than 4 cm, tumors crossing the midline, neurological deficits, and astrocytoma histology were defined as risk factors for recurrence. Patients with 2 or more of these factors have a higher risk for recurrence.[7,8] In the intergroup study; tumor size larger than 6 cm (P = .0001) and astrocytoma histology (P = .004) were defined as high-risk factors.[10] In the RTOG 9802 study, age below 40 years and gross total resection (GTR) were determined as low risk and subtotal resection (STR) and age over 40 years were categorized as high risk.[11] With the presence of 1 of these factors, the patient was determined to be at high risk.[12] When all studies are considered, age over 40 years, astrocytoma histology, tumors crossing midline, patients with neurological symptoms, and tumor size larger than 5 cm can be accepted as high risk. In Table 1, treatment options according to risk groups are presented.

Chemotherapy

In the RTOG 9802 study, adding 6 cycles of PCV (procarbazine, lomustine, and vincristine) regimen to postoperative 50.4 Gy RT in the high-risk group (STR and/or over 40 years of age) increased the 10-year OS from 40% to 60% and median survival from 7.8 to 13.3 years. Also in this study, PFS and OS benefits were more pronounced in patients with oligodendrogliomas and oligoastrocytomas.[11] There is also a trend toward improved PFS in astrocytomas (P = .06), but no statistical improvement was observed in OS probably because the number of patients in the astrocytoma group (65 patients) was insufficient for statistical power.[13]

The EORTC 22033-26033 randomized trial compared RT and Temozolomide (TMZ) in high-risk LGG and analyzed molecular markers. In this study, 477 patients were randomized to RT (n = 240); and TMZ (n = 237). There was no significant PFS difference between the 2 study arms, but in patients with IDH mut/non-codel tumors, RT had better PFS than TMZ (P = .0043) whereas no difference in patients with IDH mut/codel tumors.[12] Median PFS was 39 months for TMZ arm and 46 months for RT arm at 48 months of follow-up.

Considering RTOG and EORTC trials, although patient selection criteria are different, there is a remarkable difference in median PFS in favor of combined therapy (RT+PCV) arm in RTOG trial, 39 (TMZ arm), and 46 (RT arm) months versus 10.4 (RT+PCV) years.[11,12] Although the EORTC trial indicates that in a subgroup of patients with IDH mut/codel TMZ chemotherapy alone is as equally effective as RT alone in terms of PFS, the combined treatment RT + chemoterapy (RT+CT) should still be the standard treatment due to low PFS rates of TMZ or RT alone when compared to RTOG 9802 and phase 2 RTOG 0424 study, which has median PFS of 4.5 years.[11,14]

In view of the above-mentioned results, TMZ chemotherapy alone should not be preferred for high-risk LGG even if the patient with IDH mut/codel sub types owing oligodendrogliomas has the most survival benefit from the addition of PCV to RT in RTOG 9802 trial.[11] However, TMZ alone treatment may be an option for RT-ineligible patients with 1p19q co-deletion.

Table 1. Treatment Modalities by Risk Factors

Risk Factors	Treatment Modalities
Low risk	
<40 years Oligodendroglioma pathology IDH mutant Presence of 1p19q encoding No neurological symptoms	Total resection → follow-up Radiotherapy and chemotherapy (CRT) in progression
Gray zone	
>40 years Oligodendroglioma pathology Minimal residual presence or <40 years STR Asymptomatic patient	RT delayable CRT in progression
High risk	
>40 years Astrocytoma pathology Tumor size > 5 cm IDH wild type Progressed tumor	RT+CT (PCV or TMZ)

IDH, isocitrate dehydrogenase; STR, subtotal resection; RT, radiotherapy; CT, chemotherapy; PCV, procarbazine, lomustine, vincristine.

Molecular Subgroups

Clinical features are usually considered for routine risk group assessment. However, by using molecular subgroups, risk groups may be better distinguished. Integrated molecular and histological classification as stated in European Association of Neuro-Oncology (EANO) guidelines separates gliomas according to IDH mutations. Although IDH-mutant tumors are demonstrated to have a more favorable prognosis than their IDH-wild-type counterparts, cyclin-dependent kinase inhibitor 2A/B homozygous deletion (CDKN2A/B) is known as the other important negative prognostic factor for these tumors. In EANO guidelines, all IDH wild-type gliomas fall into the grade IV category, regardless of histological appearance. In addition, among IDH mutant tumors, homozygously deleted CDKN2A/B ones are also considered as grade IV.[15,16] All these subgroups of patients may be treated by RT with concomitant and adjuvant temozolomide such as glioblastoma. In molecular analysis, both RTOG (98-02) and EORTC (22033-26033) studies subgroup of patients with IDH wild-type gliomas had the worst survival.[12,17]

Furthermore, genetic DNA analyzes (IDH mutant, 1p19q coding) rule out epigenetic, phenotypic, and histological differences of LGGs. Pathological specimens of 200 patients out of 470 participating in the EORTC 22033-26033 study were analyzed with molecular and genetic expressions. This analysis was categorized into prognostic intrinsic glioma subgroups. And, it was observed that this grouping system was statistically significant for anticipating PFS outcomes. Also in this phase 3 study, genetic expression analysis of immune infiltrate was performed using immunophenoscore (IPS) for the first time. This scoring system was previously used in melanoma patients to estimate the tumor subgroups that respond to checkpoint inhibitors. LGGs had low IPS score (P = .004), which suggested poor response rates to immunotherapies.[17]

Most likely in the future, the molecular subtype groups in the EORTC and RTOG study will be determined and evaluations will be made in terms of treatment or follow-up according to these groups.

Treatment Selection According to Risk Groups

In the high-risk group, combined RT and CT are recommended to achieve improved PFS and OS.[14] In the low-risk group, follow-up is recommended until progression. RT can be also postponed until progression for patients in the gray zone, who are older than 40 years of old with no or minimal residue, with oligodendroglial (1p19q co-deletion, IDH mutant) histopathology, and for asymptomatic patients younger than 40 years old after STR without additional unfavorable features (Table 1).[6] When progression is detected, surgery and postoperative RT should be considered.

Adjuvant treatment decisions should be assessed by a multidisciplinary board by taking all pathological, radiological, and clinical features into account for each patient.

RT Volume

In EORTC 22845 study, 45 Gy with a 2 cm margin and 54 Gy with a 1 cm margin were applied to the preoperative computed tomography (CT) tumor images.[7] In the RTOG 9802 study, a single volume was determined and a dose of 54 Gy was defined according to the abnormality in the T2-weighted MRI signal.[18] In reference studies of LGG, the treatment volume was mostly determined using two-dimensional and three-dimensional techniques.

Today, volumetric tumor localization is performed by fusing MRIs with simulation CT images. Based on T2 FLAIR images, the primary tumor is contoured as gross tumor volume (GTV). For the microscopic disease coverage, the clinical target volume is determined by giving a 1 cm margin to GTV. Planning target volume is created by giving a 3-5 mm margin for daily set-up errors. Intensity-modulated radiotherapy technique is used.

Acute–Chronic Side Effects

Acute side effects of radiotherapy are hair loss and increased intracranial pressure. Signs of increased intracranial pressure are headache, vomiting without nausea, and paralysis of the eye muscles. Chronic side effects vary depending on the treatment modality, tumor location, treatment dose, and normal tissue tolerance doses. Since extended survivals are expected in LGGs, there is concern about neurocognitive impairment due to RT.[19]

The negative neurocognitive effects of brain irradiation are observed in patients who had whole-brain irradiation or prophylactic cranial irradiation, which is used in brain metastases, medulloblastoma, and leukemias. The neurocognitive decline is the main reason for omitting or delaying radiotherapy in LGGs. Besides RT, it was shown that tumor progression also had a negative effect on neurocognitive functions (NCF).[20] On the other hand, neurocognitive impairment includes many subheadings and is a very difficult condition to test objectively, so studies on this subject are very limited. Researchers from the Netherlands tested the cognitive effect in LGGs using neuropsychological tests. They investigated the neurocognitive effects by questioning neuropsychological tests at regular intervals to 195 LGG patients, as well as to 100 hematological malignancy patients and to 100 healthy volunteers. This study was presented in 3 important articles over time. In the first article, it was reported that when the daily dose fraction of radiotherapy exceeded 2.2 Gy, it impaired cognitive functions. These adverse effects were not observed in patients who had smaller daily RT fraction sizes. It was also determined that the use of anti-epileptic drugs negatively affected NCF. In the second study, the interaction between groups was examined and it was shown that patients with LGG had worse neurocognitive scores than patients with hematological malignancies, and the hematological malignancies group had worse neurocognitive scores than the healthy volunteers.[21] Their last study included a population with longer follow-up but a smaller sample

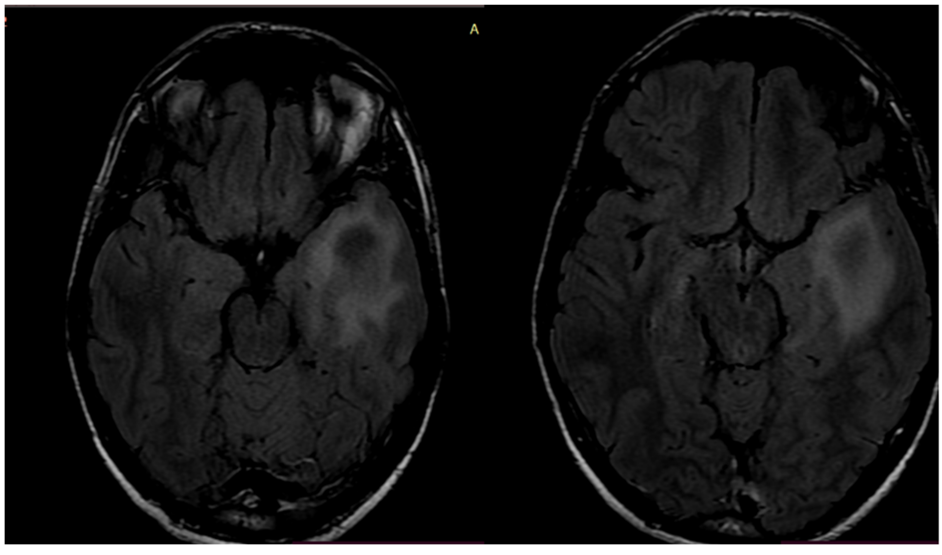

Figure 1. Preoperative T2 FLAIR signal.

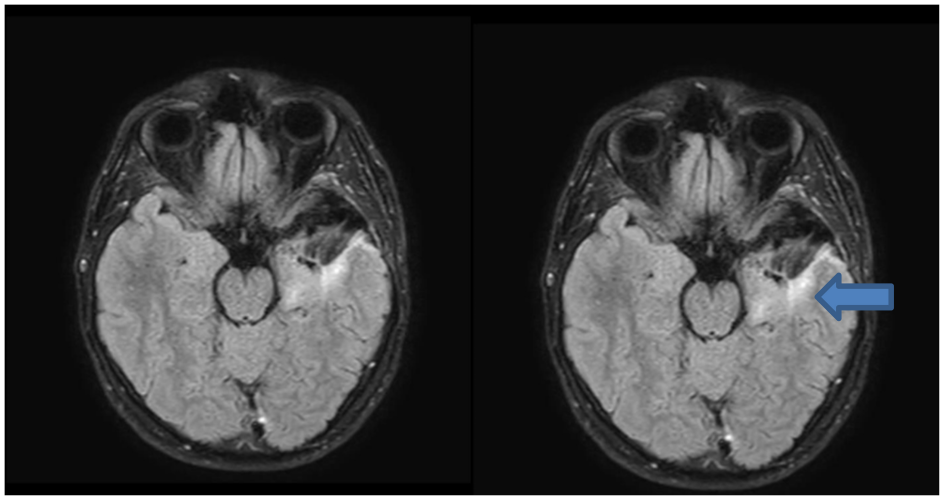

Figure 2. Postoperative T2 FLAIR signal (presence of postoperative residue).

size due to death or progression. In the last study, they showed that radiotherapy caused neurocognitive impairment independent of the daily fraction dose and their findings were accompanied by a T2 signal increase due to demyelination in the MRG.[22]

The other important treatment-related factors that determine the negative effects of radiotherapy are total dose and irradiated volume. In the EORTC study, the radiotherapy doses of 45 Gy and 59.4 Gy were compared for the quality-of-life outcome. In questionnaires, a limited deterioration in the quality of life was reported in the high-dose arm.[23] Klein et al[24] analyzed the EORTC 22033-26033 trial in terms of neurocognitive function. They included 52 patients from the RT arm and 46 patients from the TMZ arm. It has been reported that the effects of RT and TMZ on NCF are similar after 1 year. In the same study, it was shown that RT volume did not affect memory at the end of 1 year.[24]

When evaluated in terms of volume, the dose received by the hippocampus is noteworthy. Gondi et al[25] investigated the hippocampus dose and NCF effect in patients with LGG and benign brain tumors and suggested that NCF is affected if the dose is received by 40% of the bilateral hippocampus above 7.3 Gy. Because of its small sample size, it is not a widely accepted dose-volume limitation, but it can be considered in treatment planning.[25]

Besides RT, there are many factors causing neurocognitive deterioration in patients with LGGs, such as tumor progression, surgical intervention, and anti-epileptics. NCF deterioration cannot be attributed to RT alone. In patients with a high progression probability, it is not advised to postpone RT in the name of protecting neurocognitive functions.

Response Evaluation

Patients who are treated with RT or followed up after surgery should be evaluated with cranial MRI every 3 months for the first 2 years. They should be followed by MRI every 6 months for 5 years and annually thereafter until death.

Recurrence or progression is evaluated according to the Response Assessment in Neuro-Oncology (RANO) criteria. In RANO criteria; worsening in clinical status, new lesions, and/or increased signal in T2 FLAIR are defined as progression. Tumor size reduction of 25%-50% in T1 contrast signals and a similar appearance or decrease in T2 FLAIR signals are considered a stable disease.[26] LGGs are slow progressing tumors. To detect progression in follow-up, it is recommended to compare follow-up MRIs with the initial reference MRIs, not with the previous control. Figure 1, 2, and 3 show the consecutive MRI images of an LGG patient who had progression in the postoperative follow-up and received RT after the second surgery.

Conclusion

Active follow-up is recommended for LGG patients. The low-risk group patients will progress eventually, and this progression can be detected in 3-10 years. When progression is detected, surgery should be considered first, and then, postoperative RT+CT should be applied. Postoperative RT and CT should be the standard approach for high-risk patients. It is recommended to make adjuvant treatment

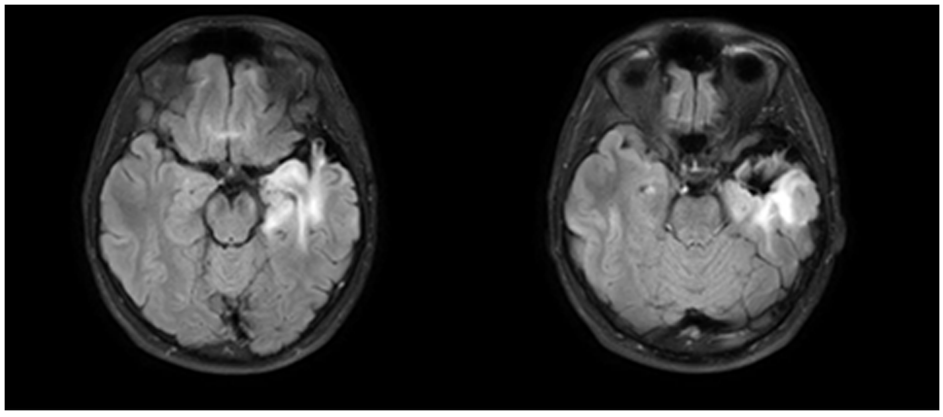

Figure 3. Progression on follow-up T2 FLAIR signal.

decision by evaluating the clinical, pathological, and radiological characteristics of the patient in a multidisciplinary manner.

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