Proposed therapeutic strategy for adult low-grade glioma based on aggressive tumor resection

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OBJECT There is no standard therapeutic strategy for low-grade glioma (LGG). The authors hypothesized that adjuvant therapy might not be necessary for LGG cases in which total radiological resection was achieved. Accordingly, they established a treatment strategy based on the extent of resection (EOR) and the MIB-1 index: patients with a high EOR and low MIB-1 index were observed without postoperative treatment, whereas those with a low EOR and/or high MIB-1 index received radiotherapy (RT) and/or chemotherapy. In the present retrospective study, the authors reviewed clinical data on patients with primarily diagnosed LGGs who had been treated according to the above-mentioned strategy, and they validated the treatment policy. Given their results, they will establish a new treatment strategy for LGGs stratified by EOR, histological subtype, and molecular status.

METHODS One hundred fifty-three patients with diagnosed LGG who had undergone resection or biopsy at Tokyo Women's Medical University between January 2000 and August 2010 were analyzed. The patients consisted of 84 men and 69 women, all with ages ≥ 15 years. A total of 146 patients underwent surgical removal of the tumor, and 7 patients underwent biopsy.

RESULTS Postoperative RT and nitrosourea-based chemotherapy were administered in 48 and 35 patients, respectively. Extent of resection was significantly associated with both overall survival (OS; $p = 0.0096$) and progression-free survival (PFS; $p = 0.0007$) in patients with diffuse astrocytoma but not in those with oligodendroglial subtypes. Chemotherapy significantly prolonged PFS, especially in patients with oligodendroglial subtypes ($p = 0.0009$). Patients with a mutant *IDH1* gene had significantly longer OS ($p = 0.034$). Multivariate analysis did not identify MIB-1 index or RT as prognostic factors, but it did identify chemotherapy as a prognostic factor for PFS and EOR as a prognostic factor for OS and PFS.

CONCLUSIONS The findings demonstrated that EOR was significantly correlated with patient survival; thus, one should aim for maximum tumor resection. In addition, patients with a higher EOR can be safely observed without adjuvant therapy. For patients with partial resection, postoperative chemotherapy should be administered for those with oligodendroglial subtypes, and repeat resection should be considered for those with astrocytic tumors. More aggressive treatment with RT and chemotherapy may be required for patients with a poor prognosis, such as those with diffuse astrocytoma, 1p/19q nondeleted tumors, or *IDH1* wild-type oligodendroglial tumors with partial resection.

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KEY WORDS low-grade glioma; surgical resection; survival; therapeutic strategy; tumor subtype

LOW-GRADE glioma (LGG) is a slowly progressive yet invasive tumor that generally arises in young adults.¹¹ However, about half of all LGG cases eventually progress to malignant transformation, and in such cases, the prognosis is dismal.⁸ There was no standard therapeutic

strategy for LGG; however, the tumor is often resected with or without subsequent fractionated radiotherapy (RT) and chemotherapy using nitrosourea or temozolomide.^{5,9,15}

Recently, the significance of the extent of resection (EOR) has been reported for LGG,^{12,14,18,19,25} and maxi-

ABBREVIATIONS ACNU = nimustine hydrochloride; EOR = extent of resection; EORTC = European Organisation for Research and Treatment of Cancer; LGG = low-grade glioma; OS = overall survival; PCV = procarbazine, lomustine, vincristine; PFS = progression-free survival; RT = radiotherapy.

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maximum resection has recently been proposed as the standard protocol. However, no randomized trial has examined the effect of EOR on the survival of patients with LGG. The European Organisation for Research and Treatment of Cancer (EORTC) 22845 randomized trial showed that early RT for LGG prolonged progression-free survival (PFS) but not overall survival (OS).²² Recent reports have shown that postoperative RT improved PFS but not OS in patients with LGG who had undergone partial tumor resection.^{19,25} Therefore, the effect of RT on the long-term survival of patients with LGG remains controversial.

Moreover, the role of chemotherapy in LGG is complicated. Although combination chemotherapy with procarbazine, lomustine, and vincristine (PCV) demonstrated promising results in the 1p/19q codeleted oligodendroglial tumors^{1,3} in the early 2000s, its long-term efficacy was disproved in the mid 2000s.^{2,23} More recent long-term results of a randomized trial (EORTC 9802) indicated both that the RT+PCV therapy prolonged PFS but not OS in patients with LGG and that this therapy may be beneficial for 2-year survivors.²¹ The role of chemotherapy in diffuse astrocytoma is unclear, and no controlled clinical trial has focused on diffuse astrocytoma. Recent developments in molecular analysis, especially for the 1p/19q locus and the *IDH1* (*isocitrate dehydrogenase 1*) gene, have allowed more convenient molecular subclassification.¹⁰ Furthermore, the above-mentioned factors have prognostic and predictive value for several tumor subtypes. Thus, LGG treatment should be decided based on the tumor's histological and molecular characteristics.

Since 2000, our institute has established “information-guided surgery” using intraoperative MRI and initiated maximum resection for gliomas.^{6,13} We hypothesized that adjuvant therapy might not be necessary for LGGs if total radiological resection was achieved. Additionally, as the E3 ubiquitin-protein ligase MIB-1 labeling index is generally proportional to the malignancy of gliomas,²⁴ we hypothesized that a LGG with a higher MIB-1 index might require postoperative therapy. Thus, we established the following treatment strategy based on EOR and the MIB-1 index: patients with a high EOR and low MIB-1 index were observed without postoperative treatment, whereas those with a low EOR and/or high MIB-1 index received RT and/or chemotherapy.

In the present retrospective study, we reviewed the clinical data of patients with primarily diagnosed LGG who had been treated with the above-mentioned strategy, and we validated the treatment policy. We then established a new treatment strategy for LGG stratified by EOR, histological subtype, and molecular status.

Methods

Patient Population

One hundred fifty-three patients, including 84 males and 69 females (ages ≥ 15 years), who had been diagnosed with LGG and had undergone resection or biopsy at Tokyo Women's Medical University between January 2000 and August 2010 were analyzed. Patients who had undergone prior resection of the tumor were excluded; however, those who had undergone previous biopsy performed as part of a

diagnostic workup leading to the eventual surgical removal of the tumor at our institution were eligible for analysis. Patients with neurofibromatosis Type 1, pleomorphic xanthoastrocytoma, or infratentorial lesions were excluded from the study. Tumor grading and pathological diagnosis were performed according to the WHO guidelines. Clinical data were collected from patient records and telephone interviews. Two outcome measures were assessed: OS and PFS. Overall survival was defined as the time between initial surgery and death, whereas PFS was defined as the time between initial surgery and the demonstration of an unequivocal increase in tumor size on follow-up imaging and obvious clinical deterioration. Patients with no known progression were censored as of their last visit and/or scan date.

Molecular Analysis

Codeletion of 1p/19q was analyzed using the fluorescence in situ hybridization method. Mutation of *IDH1* was investigated by immunohistochemical analysis of paraffin-embedded surgical specimens using anti-IDH1-R132S antibody (Dianova).

Treatment

A total of 146 patients underwent surgical removal of the tumor. Maximum resection of the T2 high-signal-intensity lesion was performed using an updated navigation system and intraoperative MRI.¹³ Seven patients underwent biopsy. Postoperative treatment was conducted as follows (Table 1): patients with an EOR $\geq 95\%$ and an MIB-1 index $< 5\%$ (Group A) were observed without any postoperative treatment, whereas those with an EOR $< 95\%$ or an MIB-1 index $\geq 5\%$ (Group B) received fractionated RT and chemotherapy with nimustine hydrochloride (ACNU) and vincristine. In 2004, we changed the therapeutic strategy for Group B, dividing the patients into two subgroups based on their 1p/19q codeletion status. Patients with 1p/19q codeletion received RT and chemotherapy with procarbazine, ACNU, and vincristine (PAV), instead of PCV because lomustine has not been approved in Japan, whereas those without 1p/19q codeletion received only RT. In 2007, we changed the EOR threshold from 95% to 90% because interim analysis showed that the OS for Group A was significantly longer than for Group B (data not shown). Forty-eight patients received extended local fractionated RT (range 50–60 Gy), and 35 received nitrosourea-based chemotherapy within 5 weeks after surgical treatment; 29 of these 35 received both RT and chemotherapy.

Volumetric Analysis

Tumor volumes, as determined from axial T2-weighted MRI, were calculated by importing DICOM (Digital Imaging and Communications in Medicine) images from MRI to Leksell GammaPlan software (Elekta). Extent of resection was calculated as follows: (preoperative tumor volume – postoperative tumor volume)/preoperative tumor volume.

Statistical Analysis

Overall survival and PFS were estimated using the Kaplan-Meier method. A log-rank test was used to evalu-

TABLE 1. Treatment strategy for LGGs in adults at a single institution in 2000–2010

Years	Group A		Group B	
	Pretreatment Factors	Treatment	Pretreatment Factors	Treatment
2000–2003	EOR $\geq$ 95% & MIB-1 <5%	Observation	EOR <95% or MIB-1 $\geq$ 5%	RT+ACNU/VCR
2004–2006	EOR $\geq$ 95% & MIB-1 <5%	Observation	EOR <95% or MIB-1 $\geq$ 5% & 1p19q codeletion (–)	RT
			EOR <95% or MIB-1 $\geq$ 5% & 1p19q codeletion (+)	RT+PAV
2007–2010	EOR $\geq$ 90% & MIB-1 <5%	Observation	EOR <90% or MIB-1 $\geq$ 5% & 1p19q codeletion (–)	RT
			EOR <90% or MIB-1 $\geq$ 5% & 1p19q codeletion (+)	RT+PAV

PAV = procarbazine, ACNU, vincristine; VCR = vincristine; (+) = positive codeletion status; (–) = negative codeletion status.

ate the importance of prognostic factors that may affect survival. Data analysis was performed using the JMP statistical software (SAS Inc.). Univariate analyses for OS and PFS were performed using Cox proportional-hazards modeling. Variables that were statistically significant or showed borderline significance on univariate analysis were further analyzed with multivariate analysis using Cox proportional-hazards modeling. Hazard ratios and 95% confidence intervals are reported with the 2-tailed probability values. The reported probability values in the Cox model are based on the Wald test, and values < 0.05 were considered significant.

Results

The median age was 37.0 years (range 15–76 years), and the median preoperative Karnofsky Performance Scale score was 100 (range 70–100). Forty-nine patients (32.0%) had diffuse astrocytoma, 45 (29.4%) had oligoastrocytoma, and 59 (38.6%) had oligodendroglioma. The median MIB-1 labeling index was 4.2% (range 0.3%–21.0%). The median time to progression was 7.4 years. Mutation of *IDH1* (R132S) was found in 111 (75.0%) of 148 patients analyzed. Most of the oligodendroglial subtypes and about half of the astrocytic tumors had *IDH1* mutation: 34 (79.1%) of 43 oligoastrocytomas, 52 (88.1%) of 59 oligodendrogliomas, and 25 (54.3%) of 46 diffuse astrocytomas. Codeletion of 1p/19q was detected in 63 (56.8%) of 111 patients investigated, including 4 (15.4%) of 26 with diffuse astrocytomas, 21 (60.0%) of 35 with oligoastrocytomas, and 38 (76.0%) of 50 with oligodendrogliomas. The 5-year and 10-year OS rates for all patients were 95.1% and 85.4%, respectively.¹⁴

Extent of Resection and Prognosis

As reported in our previous paper, both OS and PFS were significantly longer in patients with $\geq$ 90% EOR (Fig. 1A and B).¹⁴ When patients were divided into the subgroups of diffuse astrocytoma and oligodendroglial subtypes, EOR was significantly associated with both OS ($p = 0.0096$) and PFS ($p = 0.0007$) in patients with diffuse astrocytoma (Fig. 1C and D). On the other hand, EOR did not affect OS and PFS in patients with oligodendroglial subtypes (Fig. 1E and F).

Radiotherapy and Prognosis

Postoperative RT was performed in 48 patients, includ-

ing 19 (38.8%) of 49 with diffuse astrocytomas, 18 (40.0%) of 45 with oligoastrocytomas, and 11 (18.6%) of 59 with oligodendrogliomas. Radiotherapy did not correlate with OS ($p = 0.054$) and PFS ($p = 0.69$) in the analysis of all patients (Fig. 2A and B), and subgroup analysis did not show a survival benefit with RT in patients with either diffuse astrocytoma or oligodendroglial subtypes (Fig. 2C–F). Patients with oligodendroglial subtypes who received postoperative RT had longer PFS ($p = 0.02$), whereas those with diffuse astrocytoma who received RT exhibited a trend toward shorter PFS, although the relationship did not reach statistical significance. However, the effect of RT on oligodendroglial subtypes might be confounded by chemotherapy, because chemotherapy, not RT, was identified as a prognostic factor for PFS on multivariate analysis (Table 2).

Chemotherapy and Prognosis

Postoperative chemotherapy was administered in 35 patients, including 9 (18.4%) of 49 with diffuse astrocytomas, 16 (35.6%) of 45 with oligoastrocytomas, and 10 (16.9%) of 59 with oligodendrogliomas. In the analysis of all patients, chemotherapy significantly prolonged PFS ($p = 0.01$), but there was no correlation with OS ($p = 0.5$; Fig. 3A and B). Thus, a longer follow-up period might be required to elucidate the role of chemotherapy in patient survival. There was no association between chemotherapy and either OS ($p = 0.2$) or PFS ($p = 0.8$) in patients with diffuse astrocytoma (Fig. 3C and D), whereas chemotherapy was strongly associated with PFS ($p = 0.0009$) in patients with oligodendroglial subtypes (Fig. 3F). As there were only a few deaths among the patients with oligodendroglial subtypes, it was difficult to clarify the effect of chemotherapy on OS (Fig. 3E). Therefore, our findings recommend chemotherapy in patients with oligodendroglial subtypes who undergo partial tumor resection. On the other hand, repeated surgery aiming at additional resection may be necessary in patients with diffuse astrocytoma whose EOR was low in the first surgery.

Molecular Status and Prognosis

Patients with codeletion of 1p/19q locus showed significantly longer PFS ($p = 0.0048$), but no OS differences ($p = 0.4$) were observed between patients with and without such a deletion, probably because of the small number of death events (Fig. 4A and B). Chemotherapy significantly prolonged PFS in patients with oligodendroglial subtypes regardless of their 1p/19q codeletion status (data not shown).

FIG. 1. Overall survival (A) and PFS (B) for all patients, according to EOR. Overall survival (C) and PFS (D) for patients with diffuse astrocytoma, according to EOR. Overall survival (E) and PFS (F) for patients with oligodendroglial subtypes, according to EOR. N or n = number of patients. Asterisks indicate significant p values.

In the analysis of all patients, *IDH1* status was significantly associated with OS ($p = 0.034$) but not with PFS ($p = 0.12$; Fig. 4C and D). In a subgroup analysis, *IDH1* status

did not correlate with either OS or PFS in patients with diffuse astrocytoma (data not shown).

Interestingly, EOR was strongly associated with OS in

FIG. 2. Overall survival (A) and PFS (B) for all patients, according to treatment with (+) or without (-) RT. Overall survival (C) and PFS (D) for patients with diffuse astrocytoma, according to treatment with or without RT. Overall survival (E) and PFS (F) for patients with oligodendroglial subtypes, according to treatment with or without RT.

TABLE 2. Results of univariate and multivariate analysis

Factor	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p Value	HR	95% CI	p Value
OS						
Age in yrs: ≥ 50 vs < 50	5.43	1.55–21.30	0.0089*	5.38	1.46–22.10	0.0121*
Tumor diameter in cm: ≥ 5 vs < 5	1.52	0.43–5.97	0.5087	1.08	0.29–4.43	0.9026
Tumor subtype: DA vs O/OA	4.98	1.37–23.27	0.0143*	5.23	1.33–26.08	0.0172*
RT: no vs yes	3.30	0.07–1.08	0.0656	0.34	0.06–1.97	0.2234
Chemotherapy: no vs yes	0.68	0.19–2.70	0.5667	0.99	0.14–4.95	0.8978
PFS						
Age (yrs): ≥ 50 vs < 50	1.58	0.80–2.93	0.1757	1.41	0.70–2.67	0.3149
Tumor diameter in cm: ≥ 5 vs < 5	1.59	0.89–2.89	0.1122	1.89	1.02–3.55	0.0428*
Tumor subtype: DA vs O/OA	2.08	1.16–3.72	0.0140*	1.86	1.00–3.40	0.0485*
RT: no vs yes	1.1	0.60–2.12	0.7422	0.73	0.33–1.72	0.463
Chemotherapy: no vs yes	2.27	1.13–5.07	0.0195*	3.17	1.23–6.56	0.0161*

DA = diffuse astrocytoma; O = oligodendroglioma; OA = oligoastrocytoma.

* Statistically significant.

patients with wild-type *IDH1*, although it did not affect OS in patients with *IDH1* mutation (data not shown). Thus, our results indicated extensive resection for patients without *IDH1* mutation. However, chemotherapy significantly prevented recurrence in patients with mutant *IDH1* ($p < 0.0001$) but did not affect PFS ($p = 0.051$) in those with wild-type *IDH1* (Fig. 4E and F). Thus, our findings suggest that repeat surgery should be considered for patients with wild-type *IDH1* who have partial tumor removal in their first operation.

Univariate and Multivariate Analysis

In this study, we examined univariate and multivariate modeling using the following parameters: patient age, tumor diameter, tumor subtype, RT, and chemotherapy. Among these factors, multivariate analysis identified tumor subtype and chemotherapy for PFS, suggesting that the role of chemotherapy in preventing a recurrence depends on the tumor subtype (Table 2). However, the parameters identified as significant for OS were the conventional risk factors of age and tumor subtype, but not chemotherapy.

FIG. 3. Overall survival (A) and PFS (B) for all patients, according to treatment with or without chemotherapy. Overall survival (C) and PFS (D) for patients with diffuse astrocytoma, according to treatment with or without chemotherapy. Overall survival (E) and PFS (F) for patients with oligodendroglial subtypes, according to treatment with or without chemotherapy.

FIG. 4. Overall survival (A) and PFS (B) for all patients, according to status of 1p/19q codeletion. Overall survival (C) and PFS (D) for all patients, according to status of *IDH1* mutation. Progression-free survival for patients with mutant (mt) *IDH1* (E) and wild-type (WT) *IDH1* (F), according to treatment with or without chemotherapy.

When EOR was added as a candidate factor for multivariate analysis, only EOR was selected for PFS, whereas EOR and age were selected for OS.¹⁴ Tumor subtype was not selected in the analysis including EOR, suggesting that EOR is a strong prognostic factor regardless of tumor subtypes. The limitation of the multivariate analysis in this study is the confounding bias between EOR and RT/chemotherapy, because patients with a high EOR did not receive RT or chemotherapy and these factors cannot be included at the same time.

Discussion

New Treatment Strategy for LGG

In our previous report, we showed that EOR was strongly associated with OS in patients with LGG but that the MIB-1 index was not associated with OS in these patients.¹⁴ In the present study, the associations of RT, chemotherapy, and molecular status with patient survival were analyzed in detail. Given our results, we will update our treatment strategy for LGG, including 3 major changes (Fig. 5). First, the MIB-1 index will be excluded because none of the analyses showed statistical differences in patient survival according to this index. Second, patients with a low EOR (Group B) will be further divided into 2 subgroups according to histological subtypes, as there were significant differences in the response to chemotherapy between astrocytic and oligodendroglial tumors. Finally, treatment of patients with oligodendroglial subtypes will be stratified into 2 categories as follows: chemotherapy only for patients with 1p/19q codeletion and/or mutant *IDH1*, and RT and chemotherapy for those who had neither 1p/19q codeletion nor an *IDH1* mutation.

This stratification was performed given the worse prognosis in the latter group.

In our prospective case series, we stratified postoperative treatment by EOR instead of age. Age is among the previously described risk factors for a poor prognosis in cases of LGG.¹⁶ As a result, patients with an EOR $\geq 90\%$ achieved excellent clinical courses regardless of their age, with 5- and 10-year OS rates of 97.8% and 95.3%, respectively. Although another clinical trial stratified adjuvant therapy by EOR and age,²¹ our results strongly suggested that patients with a high EOR could be safely observed without postoperative therapy and that maximum tumor resection should be aimed for in LGG. However, EOR did not affect OS and PFS in patients with oligodendroglial subtypes (Fig. 1E and F). The underlying explanation for this result might be that chemotherapy was largely effective in preventing recurrences of oligodendroglial tumors (Fig. 3F). Further, patients with oligodendroglial subtypes who received chemotherapy had a low EOR.

In this study, chemotherapy significantly prolonged PFS according to both univariate and multivariate analyses (Table 2). Subgroup analyses based on histological subtypes revealed that the correlation between chemotherapy and PFS was significant in patients with oligodendroglial subtypes, but not in patients with diffuse astrocytoma (Fig. 3). Thus, when EOR is less than 90%, chemotherapy should be recommended for oligodendroglial subtypes, but repeat resection should be considered in patients with diffuse astrocytoma. A good example of such a scenario involves cases of LGG located in an eloquent area with biopsy or partial resection performed at another institution. It is possible to perform repeated sur-

FIG. 5. Therapeutic strategy for LGG stratified by EOR, histological subtype, and molecular status. Patients with $\geq 90\%$ EOR can be safely observed regardless of their tumor subtype. Patients with $< 90\%$ EOR are divided into two groups, diffuse astrocytoma and oligodendroglial subtypes, and those with diffuse astrocytoma are recommended for repeat surgery, whereas those with oligodendroglial subtypes are treated with chemotherapy with or without RT according to their molecular status. Cx = chemotherapy; Rx = radiation; TMZ = temozolomide. Modified from Nitta et al: *Neurol Med Chir (Tokyo)* 53:447–454, 2013. Published with permission.

gery using awake craniotomy to achieve maximum tumor resection for these patients.⁴ Furthermore, it is noteworthy that chemotherapy significantly prolonged PFS in patients with mutant *IDH1* ($p < 0.0001$). In contrast, patients with wild-type *IDH1* (mostly in cases of the astrocytic subtype) who had received chemotherapy showed a poorer prognosis than those who did not receive chemotherapy (Fig. 4). This result supports the notions that 1) patients with diffuse astrocytoma harboring wild-type *IDH1* would not benefit from chemotherapy and 2) tumor resection has the strongest impact on astrocytic tumors.

Our multivariate analysis did not identify any significant role for RT, whereas PFS was prolonged among patients with oligodendroglial subtypes who had received RT (Fig. 2F). Since most of the patients who had received RT also received chemotherapy, this effect might be attributable to chemotherapy. Radiotherapy has been routinely administered for LGG, and the appropriate RT dosages were investigated in the 1980s and 1990s.^{7,20} However, higher doses of fractionated RT for LGG did not show a survival benefit. The EORTC 22845 trials reported that early RT did not affect OS,²² and recent retrospective analyses showed that postoperative RT did not prolong OS.^{19,25} On the other hand, Pouratian et al. showed improved outcomes for older patients receiving postoperative RT,¹⁷ and Youland et al. reported that patients in the 1980s and 1990s in whom EOR was lower may have benefited from

RT.²⁵ Thus, there might be a subgroup that benefits from postoperative RT. Therefore, a randomized clinical trial is necessary to clarify the role of postoperative RT. In our new strategy, RT is only administered to patients with a poor prognosis, such as those who have diffuse astrocytoma with a low EOR or those who have oligodendroglial tumors with a low EOR, without 1p/19q codeletion, and without *IDH1* mutation. Although it is reasonable to provide stronger treatment to patients with a poor prognosis, it is debatable whether both RT and chemotherapy should be administered in patients with poor-prognosis LGG. The definitive roles of RT and chemotherapy have been demonstrated in patients with anaplastic gliomas; therefore, these treatments might be more effective after malignant transformation. New therapeutic strategies might be required for patients with a poor prognosis.

This study has limitations. First, although we performed a volumetric analysis, accurate estimation of the EOR is difficult for diffuse tumors that have unclear borders. Second, since patients with a low EOR received adjuvant therapy in this study, there is strong confounding between EOR and RT/chemotherapy. Thus, it is difficult to accurately evaluate the role of RT and chemotherapy. Third, a number of patients received both RT and chemotherapy. Therefore, it is difficult to accurately compare the roles of RT and chemotherapy alone. Therefore, a controlled clinical trial will be necessary in the future.

Conclusions

The clinical management of LGG has not been standardized. Our findings demonstrated that EOR significantly correlated with patient survival; thus, we should aim for maximum tumor resection. In addition, patients with a higher EOR can be safely observed without adjuvant therapy. For those with partial resection, postoperative chemotherapy should be administered and repeat resection should be considered for those with astrocytic tumor. Patients with a poor prognosis, such as those having diffuse astrocytoma and 1p/19q nondeleted or *IDH1* wild-type oligodendroglial tumors with partial resection, may require more aggressive treatment with RT and chemotherapy.

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