CLINICAL STUDY

Tumor recurrence patterns after surgical resection of intracranial low-grade gliomas

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Abstract

Introduction Tumor recurrence patterns after resection of intracranial low-grade gliomas (LGG) generally remain obscured. The objective of the present retrospective study was their multifaceted analysis, evaluation of associated factors, and assessment of impact on prognosis.

Methods Study group comprised 81 consecutive adult patients (46 men and 35 women; median age, 37 years) with recurrent diffuse astrocytomas (DA; 51 cases) and oligodendrogliomas (OD; 30 cases). The median length of follow-up after primary surgery was 6.7 years.

Results Early (within 2 years after primary surgery) and non-early (> 2 years after primary surgery) recurrence was noted in 23 (28%) and 58 (72%) cases, respectively. Fast (≤ 6 months) and slow (> 6 months) radiological progression of relapse was noted in 31 (38%) and 48 (59%) cases, respectively. Tumor recurrence was local and non-local in 71 (88%) and 10 (12%) cases, respectively. Recurrence patterns have differed in OD, *IDH1*-mutant DA, and *IDH* wild-type DA. Early onset, fast radiological progression, and non-local site of relapse had statistically significant negative impact on overall survival of patients and were often associated with malignant transformation of the tumor (38 cases). However, in subgroup with extent of resection ≥ 90% (56 cases) no differences in recurrence characteristics were found between 3 molecularly defined groups of LGG.

Conclusions Recurrence patterns after resection of LGG show significant variability, differ in distinct molecularly defined types of tumors, and demonstrate definitive impact on prognosis. Aggressive resection at the time of primary surgery may result in more favorable characteristics of recurrence at the time of its development.

Keywords Adjuvant therapy · Fractionated radiotherapy · Low-grade glioma · Recurrence · Surgery · Survival

Introduction

Owed to invasive growth into brain parenchyma precluding radical surgical removal, and resistance to irradiation and chemotherapy the vast majority of gliomas are currently considered as incurable disease, thus relapse of the neoplasm can be always expected at some time point during the clinical course. High-grade gliomas recurrent after primary surgery, fractionated radiotherapy (FRT), and chemotherapy have been a subject of multiple investigations [1–6]. In contrast, much fewer studies dealt with recurrent low-grade gliomas (LGG), which may be particularly caused by their rarity and relatively favorable prognosis associated with prolonged progression-free survival (PFS) and overall survival (OS) of patients. Nevertheless, the clinical course of LGG may be unpredictable, as some of these tumors recur soon after primary treatment and/or undergo malignant transformation [7–15]. It is known, that approximately 80–90% of recurrences of LGG are local [7, 16], but other characteristics of relapse in such cases (e.g., time of onset, speed of progression, associations with molecular features of the tumor, extent of resection [EOR], and administration of postoperative FRT and chemotherapy) and their prognostic

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significance are mostly remain obscured, although it may have an important implication for choice of the optimal mode and timing of the adjuvant treatment after primary surgery. The objective of the present retrospective study was multifaceted analysis of recurrence patterns after resection of intracranial LGG along with evaluation of associated factors and assessment of the general impact on the outcome.

Materials and methods

From January 2000 till June 2013, 227 consecutive adult patients (age ≥ 18 years) underwent surgical resection of newly diagnosed intracranial LGG in the Department of Neurosurgery of the Tokyo Women's Medical University. Out of the total cohort, 81 patients (36%) experienced tumor recurrence during follow-up and comprised study group (Table 1). During the same time span in 15 other patients histopathological diagnosis of LGG was established after tumor biopsy, but these cases were excluded from the present analysis. Study protocol was approved by the ethics committee and institutional review board of the Tokyo Women's Medical University (approval #3540-R03).

Surgical treatment

In all cases tumor resection was performed according to the concept of information-guided surgery based on the integrated analysis of various intraoperative data reflecting anatomical, functional, and histopathological characteristics of the clinical case, which presumes routine use of low-field-strength intraoperative MRI (AIRIS IITM; Hitachi Medical Corporation, Tokyo, Japan), updated neuronavigation, comprehensive intraoperative neurophysiological techniques, and histopathological monitoring of the resected tissue [17, 18]. In our practice, surgery for LGG is directed at maximum resection of the area of T2 hyperintensity with preservation of the functionally important cortical and subcortical neuronal and vascular structures. EOR was determined based on the volumetric comparison of the hyperintensity area on T2-weighted MRI performed before surgery and within 72 h thereafter.

Histopathological diagnosis

Histopathological tumor typing and grading was based on the standard criteria of the 4th edition of the World Health Organization (WHO) classification of central nervous system (CNS) tumors (2007) [19] with additional consideration of changes reflected in its updated version (2016) [20]. In particular, combined complete loss of the chromosomal arms 1p and 19q (1p/19q co-deletion) was considered as prerequisite for diagnosis of oligodendroglioma (OD) unless

Table 1 Clinical characteristics of the present series

Clinical characteristics	Values
Number of patients	81 (100%)
Patient age (years)	
Range	20–70
Median	37
Patient gender	
Men	46 (57%)
Women	35 (43%)
KPS score before primary surgery	
Range	80–100
Median	100
Tumor histology	
Diffuse astrocytoma	51 (63%)
Oligodendroglioma	30 (37%)
MIB-1 index (%)	
Range	1–21
Median	4.8
$IDH1^{R132H}$ mutation	
Present	64 (79%)
Absent	16 (20%)
Unknown	1 (1%)
1p/19q co-deletion	
Present	28 (35%)
Absent	46 (57%)
Unknown	7 (9%)
Extent of resection at primary surgery (%)	
Range	20–100
Median	90
Postoperative FRT	
Yes	23 (28%)
No	58 (72%)
Postoperative chemotherapy	
Yes	15 (19%)
No	66 (81%)

FRT fractionated radiotherapy, *KPS* Karnofsky performance scale

cytogenetic testing was not done. Immunohistochemical staining for Ki-67 with MIB-1 antibodies was performed in all cases, and for encoded protein products of mutant $IDH1^{R132H}$ in 80 tumors (99%). Assessment of 1p/19q co-deletion was done in 74 tissue samples (91%).

Adjuvant therapy

Strategy of postoperative treatment for LGG was generally based on the previously reported protocol adopted in our practice [21]. Briefly, in cases with EOR ≥ 90% adjuvant therapy was usually omitted and patients underwent observational follow-up with regular MRI examinations. In cases with EOR < 90%, postoperative local FRT alone (total dose,

50 Gy; 25 fractions; 2 Gy per fraction) or combined with chemotherapy (nimustine hydrochloride [ACNU], 80 mg/m^2 i.v. once in 8 weeks; 6–8 cycles in total) was recommended routinely in cases of 1p/19q non-codeleted and co-deleted tumors, respectively [21]. Nevertheless, due to different reasons even after EOR ≥ 90% some patients, considered as "high-risk," received adjuvant therapy, whereas in few cases with EOR < 90% it was delayed until tumor recurrence.

Follow-up

Patients were followed with regular clinical and radiological evaluations scheduled each 3 months during first year after surgery and each 4–6 months thereafter. In case of clinical deterioration examination was done urgently. The median length of follow-up was 6.7 years (range 1.0–14.8 years).

Diagnosis of recurrence

Radiological diagnosis of tumor recurrence was generally based on criteria of Response Assessment in Neuro-Oncology (RANO) working group [22] and included ≥ 25% increase of the product of perpendicular diameters of the lesion or appearance of new hyperintense area(s) on T2-weigthed and/or FLAIR images not attributable to effects of adjuvant therapy, or appearance or expansion of the contrast-enhanced areas on T1-weighted images, in association with "tumor pattern" on proton magnetic resonance spectroscopy (^{1}H-MRS) and definite radioisotope uptake on positron emission tomography with ^{11}C-methionine (MET-PET). Appearance of a new area of contrast enhancement on T1-weighted MRI was considered as a sign of malignant transformation [22]. Differentiation of tumor recurrence and radiation-induced necrosis (if required) was mainly based on MET-PET. Histopathological diagnosis of tumor recurrence and malignant transformation (if presented) was established upon examination of the pathological tissue after re-resection of the lesion, which was done in 62 cases (77%).

The time of recurrence onset was defined according to date of the first MRI examination at which it was suspected. Early and non-early recurrences were considered if it were diagnosed, respectively, within 2 years or > 2 years after primary surgery. With regard to speed of progression, recurrences were categorized as fast and slow, if time interval from initial imaging changes to definitive radiological diagnosis was, respectively, ≤ 6 months and > 6 months. With regard to location, the following recurrence patterns were considered [5]: regional (in the wall of resection cavity), marginal (within 20 mm from the margin of resection cavity), distant (> 20 mm from the margin of resection cavity), multiple (several discontiguous recurrences in various brain areas), and CSF dissemination (Fig. 1). Regional and marginal recurrences were defined as local, and distant, multiple, and CSF dissemination as non-local.
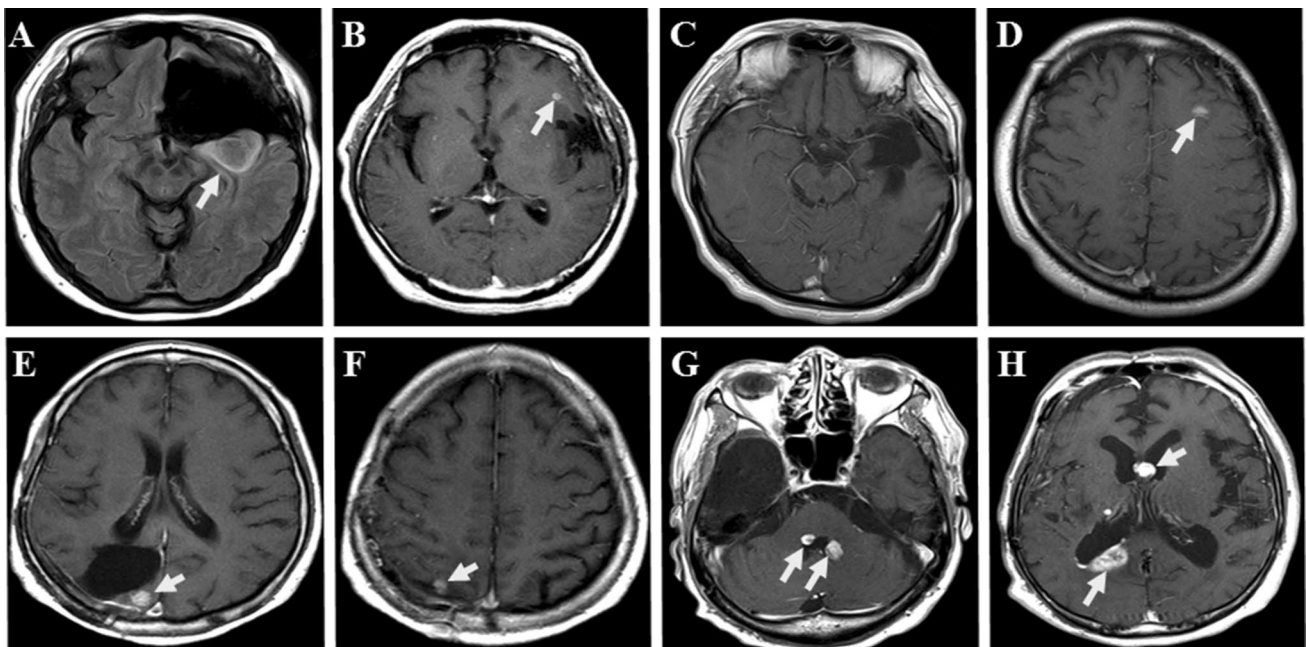

Fig. 1 Recurrence patterns of intracranial low-grade gliomas (*arrows*) with regard to location: regional (**a**), marginal (**b**), distant (**c**, **d**), multiple (**e**, **f**), and CSF dissemination (**g**, **h**)

Statistical analysis

Group comparisons were done with chi-square test. Survival analysis was performed with construction of Kaplan–Meier curves and their comparison by log-rank test. PFS and OS were calculated from the time of primary surgery. Statistically significant difference was defined if P-value of two-tailed test was < 0.05. All calculations were done with commercially available software JMP® Pro 13, version 13.0.0 (SAS Institute Inc., Cary, NC, USA).

Results

The study group comprised 51 DA and 30 OD. Median MIB-1 index was 4.8% (range 1–21%). Immunopositivity for mutant $IDH1^{R132H}$ was identified in 64 cases (79%) and 1p/19q co-deletion was revealed in 28 cases (35%). The group of DA included 32 cases of $IDH1^{R132H}$ immunopositive and 1p/19q non-codeleted tumors, 13 cases of $IDH1^{R132H}$ immunonegative and 1p/19q non-codeleted tumors, 1 case of $IDH1^{R132H}$ non-tested and 1p/19q non-codeleted tumor, as well as 2 cases of $IDH1^{R132H}$ immunopositive and 3 cases of $IDH1^{R132H}$ immunonegative tumors which were not tested for 1p/19q status, but histologically were diagnosed as DA. The group of OD comprised 28 cases of $IDH1^{R132H}$ immunopositive and 1p/19q co-deleted tumors, and 2 cases of $IDH1^{R132H}$ immunopositive tumors which were not tested for 1p/19q status, but histologically were diagnosed as OD.

The median EOR at primary surgery was 90% (range 20–100%); in 56 patients (69%) EOR was ≥ 90%. There was no statistically significant difference of EOR between molecularly defined groups of tumors. Overall, 23 patients received postoperative FRT and 15 were treated with chemotherapy.

During follow-up malignant transformation of the tumor was noted in 38 patients (47%), and was diagnosed histopathologically in 29 cases and radiologically in 9. It was encountered significantly more often in cases with EOR < 90% than with EOR ≥ 90% (64% vs. 39%; P=0.0395). Median PFS of patients in the study group was 3.3 years (range 0.4–12.0 years), median OS was 12.6 years (range 1.0–14.8 years), and actuarial 10-year OS rate was 56%.

Characteristics of tumor recurrences and associated factors

Tumor recurrence characteristics and associated factors in the entire study group are presented in Table 2.

Early tumor recurrence was noted in 23 cases (28%) and was diagnosed at a median interval of 1.0 year after primary surgery (range 0.4–1.9 years). Non-early tumor recurrence was noted in 58 cases (72%) cases and was diagnosed at a median interval of 4.1 years after primary surgery (range 2.1–11.9 years). Early tumor recurrence was identified more frequently in men (P=0.0140), in cases of DA (P=0.0049), without $IDH1^{R132H}$ mutation (P=0.0066), absent 1p/19q co-deletion (P=0.0085), and in presence of malignant transformation of the neoplasm during follow-up (P=0.0022). OS of patients with early recurrence of LGG (median, 5.1 years; range 1.0–13.5 years) was shorter than in cases with non-early recurrence (median not reached; range 3.4–14.8 years) and this difference was statistically significant (P=0.0005; Fig. 2a).

In 2 cases (2%) speed of radiological progression of tumor recurrence could not be assessed because of lack of corresponding images. Fast recurrence progression was noted in 31 cases (38%) and lasted at median 0.2 month (range 0.0–5.5 months) from the initial imaging changes to definitive radiological diagnosis of relapse. Slow recurrence progression was noted in 48 cases (59%) and lasted at median 16.1 months (range 6.2–95.5 months) from the initial imaging changes to definitive radiological diagnosis of relapse. Fast recurrence progression was noted more frequently in cases without $IDH1^{R132H}$ mutation (P=0.0266), EOR < 90% (P < 0.0001), if postoperative FRT was administered (P=0.0004), and in presence of malignant transformation of the neoplasm during follow-up (P=0.0011). OS of patients with fast recurrence progression (median, 6.7 years; range 1.0–14.1 years) was shorter than in cases with slow recurrence progression (median not reached; range 1.3–14.8 years) and this difference was statistically significant (P=0.0021; Fig. 2b).

With regard to location, tumor recurrence was defined as regional in 67 cases (83%), marginal in 4 (5%), distant in 4 (5%), and multiple in 5 (6%); CSF dissemination was noted in 1 case (1%). Local tumor recurrence (71 cases) was identified more frequently in cases of OD (P=0.0096), with MIB-1 index < 5% (P=0.0313), presence of 1p/19q co-deletion (P=0.0080), EOR ≥ 90% (P=0.0331), if postoperative FRT was not administered (P < 0.0001), and without malignant transformation of the neoplasm during follow-up (P=0.0035). OS of patients with non-local recurrence of LGG (median, 5.5 years; range 1.1–7.0 years) was shorter than in cases with local recurrence (median not reached; range 1.0–14.8 years) and this difference was statistically significant (P=0.0003; Fig. 2c).

Characteristics of tumor recurrences in different types of tumors

Since molecular features of LGG were one of the most important determinants of the recurrence characteristics, comparison was done between 3 definitively determined groups of tumors, namely $IDH1^{R132H}$ immunopositive, 1p/19 co-deleted OD (Group I; N=28), $IDH1^{R132H}$

Table 2 Comparative analysis of tumor recurrence characteristics in the present series (N = 81)

Clinical and treatment parameters	Characteristics of tumor recurrence								
	Time of onset			Speed of radiological progression[a]			Location		
	Early (N = 23)	Non-early (N = 58)	P-value	Fast (N = 31)	Slow (N = 48)	P-value	Local (N = 71)	Non-local (N = 10)	P-value
Patient age			0.1419			0.1061			0.4684
< 40 years (N = 49)	11 (14%)	38 (47%)		15 (19%)	32 (41%)		44 (54%)	5 (6%)	
≥ 40 years (N = 32)	12 (15%)	20 (25%)		16 (20%)	16 (20%)		27 (33%)	5 (6%)	
Patient gender			**0.0140**			0.1199			0.1135
Man (N = 46)	18 (22%)	28 (35%)		21 (27%)	24 (30%)		38 (47%)	8 (10%)	
Woman (N = 35)	5 (6%)	30 (37%)		10 (13%)	24 (30%)		33 (41%)	2 (2%)	
KPS score before primary surgery			0.3051			0.4403			0.6434
100 (N = 46)	11 (14%)	35 (43%)		16 (20%)	29 (37%)		41 (51%)	5 (6%)	
< 100 (N = 35)	12 (15%)	23 (28%)		15 (19%)	19 (24%)		30 (37%)	5 (6%)	
Tumor histology			**0.0049**			0.1881			**0.0096**
Diffuse astrocytoma (N = 51)	20 (25%)	31 (38%)		22 (28%)	27 (34%)		41 (51%)	10 (12%)	
Oligodendroglioma (N = 30)	3 (4%)	27 (33%)		9 (11%)	21 (27%)		30 (37%)	0 (0%)	
MIB-1 index			0.6479			0.6156			**0.0313**
< 5% (N = 42)	11 (14%)	31 (38%)		15 (19%)	26 (33%)		40 (49%)	2 (2%)	
≥ 5% (N = 39)	12 (15%)	27 (33%)		16 (20%)	22 (28%)		31 (38%)	8 (10%)	
$IDH1^{R132H}$ mutation[b]			**0.0066**			**0.0266**			0.8596
Present (N = 64)	14 (18%)	50 (63%)		20 (26%)	42 (54%)		57 (71%)	7 (9%)	
Absent (N = 16)	9 (11%)	7 (9%)		10 (13%)	6 (8%)		14 (18%)	2 (3%)	
1p/19q co-deletion[c]			**0.0085**			0.3891			**0.0080**
Present (N = 28)	3 (4%)	25 (34%)		9 (12%)	19 (26%)		28 (38%)	0 (0%)	
Absent (N = 46)	18 (24%)	28 (38%)		19 (26%)	26 (36%)		36 (49%)	10 (14%)	
Extent of tumor resection at primary surgery			0.1217			**< 0.0001**			**0.0331**
≥ 90% (N = 56)	13 (16%)	43 (53%)		12 (15%)	42 (53%)		52 (64%)	4 (5%)	
< 90% (N = 25)	10 (12%)	15 (19%)		19 (24%)	6 (8%)		19 (23%)	6 (7%)	

Table 2 (continued)

Clinical and treatment parameters	Characteristics of tumor recurrence								
	Time of onset			Speed of radiological progression[a]			Location		
	Early (N = 23)	Non-early (N = 58)	P-value	Fast (N = 31)	Slow (N = 48)	P-value	Local (N = 71)	Non-local (N = 10)	P-value
Postoperative FRT			0.0580			**0.0004**			**< 0.0001**
Yes (N = 23)	10 (12%)	13 (16%)		16 (20%)	7 (9%)		14 (17%)	9 (11%)	
No (N = 58)	13 (16%)	45 (56%)		15 (19%)	41 (52%)		57 (70%)	1 (1%)	
Postoperative chemotherapy			0.8694			0.5128			0.0618
Yes (N = 15)	4 (5%)	11 (14%)		7 (9%)	8 (10%)		11 (14%)	4 (5%)	
No (N = 66)	19 (23%)	47 (58%)		24 (30%)	40 (51%)		60 (74%)	6 (7%)	
Malignant transformation of the tumor during follow-up			**0.0022**			**0.0011**			**0.0035**
Yes (N = 38)	17 (21%)	21 (26%)		22 (28%)	16 (20%)		29 (36%)	9 (11%)	
No (N = 43)	6 (7%)	37 (46%)		9 (11%)	32 (41%)		42 (52%)	1 (1%)	

FRT fractionated radiotherapy, *KPS* Karnofsky performance scale, bold, statistically significant values

[a]In 2 cases this characteristic could not be assessed because of lack of images

[b]1 case with unknown *IDH1*[R132H] mutational status was excluded from the analysis

[c]7 cases with unknown 1p/19q status were excluded from the analysis

immunopositive, 1p/19 non-codeleted DA (Group II; N = 32), and *IDH1*[R132H] immunonegative, 1p/19 non-codeleted DA (Group III; N = 13).

Risk of early recurrence was significantly lower in Group I (11%) in comparison with Groups II (34%; OR 4.37; 95% CI 1.07–17.74; P = 0.0197) and III (54%; OR 9.72; 95% CI 1.93–49.11; P = 0.0030); the difference between Groups II and III was not statistically significant (OR 2.23; 95% CI 0.6–8.27). Risk of fast recurrence progression was 32% in Group I, 32% in Group II (OR 1.01; 95% CI 0.34–3.00), and 62% in Group III (OR 3.38; 95% CI 0.86–13.30), but differences did not reach statistical significance. There was no non-local recurrences in Group I, whereas their risks in Groups II (22%) and III (15%; OR 0.65; 95% CI 0.12–3.64) did not demonstrate statistically significant difference.

Characteristics of tumor recurrences after aggressive surgery

In cases with EOR ≥ 90% at primary surgery early and non-early tumor relapses were noted in 13 (23%) and 43 (77%) cases, respectively. Early tumor recurrence was identified more frequently in men (P = 0.0104), in cases of DA (P = 0.0440), and if postoperative FRT was administered (P = 0.0121). Fast and slow recurrence progression was noted in 12 (22%) and 42 (78%) cases, respectively.

Fast recurrence progression was noted more frequently if postoperative FRT was administered (P = 0.0084) and in presence of malignant transformation of the neoplasm during follow-up (P = 0.0382). Local and non-local tumor recurrences were identified in 52 (93%) and 4 (7%) cases, respectively. Local tumor recurrence was noted more frequently in younger patients (P = 0.0439), in cases with MIB-1 index < 5% (P = 0.0379), if postoperative FRT was not administered (P < 0.0001), and without malignant transformation of the neoplasm during follow-up (P = 0.0099).

After aggressive surgery no statistically significant difference in evaluated recurrence characteristics was found between 3 molecularly defined groups of tumors. Risk of early recurrence comprised 10% in Group I, 32% in Group II (OR 4.24; 95% CI 0.79–22.85), and 29% in Group III (OR 3.60; 95% CI 0.40–32.37). Risk of fast recurrence progression was 25% in Group I, 16% in Group II (OR 0.60; 95% CI 0.14–2.62), and 43% in Group III (OR 2.25; 95% CI 0.37–13.71). There was no non-local recurrences in Group I, and their risks in Groups II (12%) and III (14%; OR 1.22; 95% CI 0.11–13.97) did not demonstrate statistically significant difference. In particular, aggressive resection has resulted in significant decrease of proportion of early recurrences in Group III, and proportions of fast progressing and non-local recurrences in Group II (Table 3).
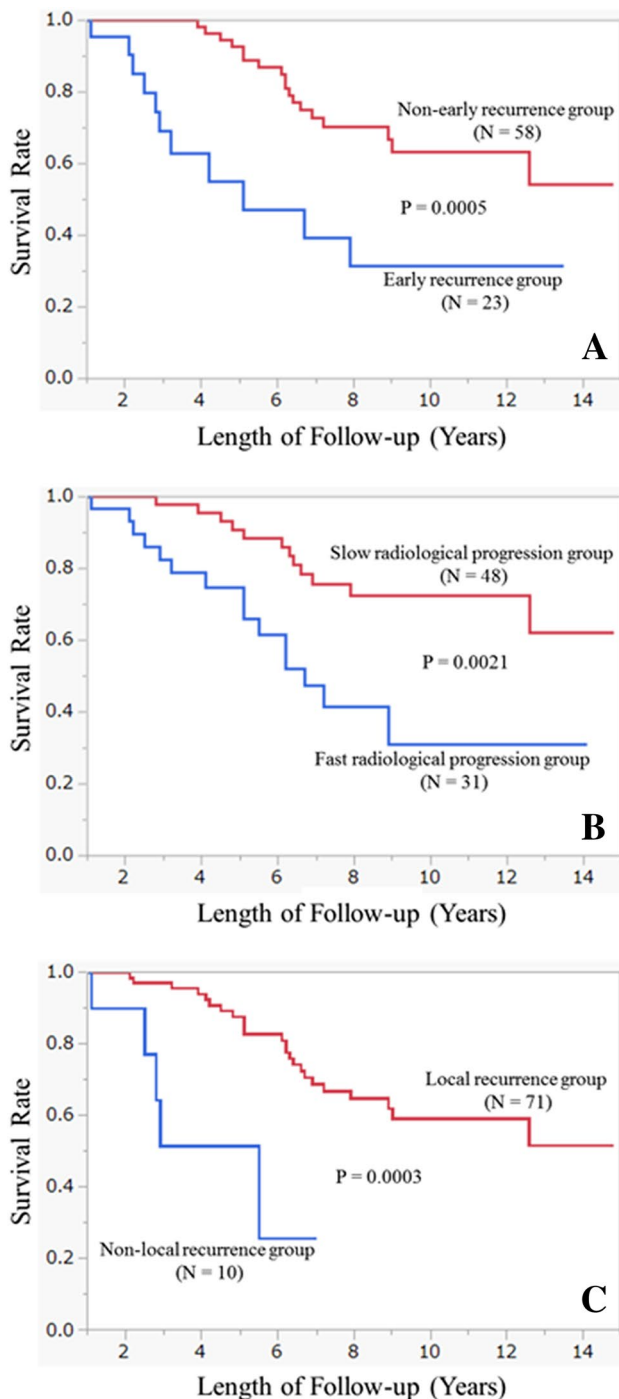
Fig. 2 Kaplan–Meier curves demonstrating comparison of overall survival rates in patients with relapsing low-grade gliomas with regard to time of onset of recurrence (**a**), speed of its radiological progression (**b**), and location (**c**)

Discussion

Median OS of patients with LGG varies from 2.7 to 16.7 years [7, 14, 23–26]. The mostly accepted prognostic factors are age at diagnosis, Karnofsky performance scale

(KPS) score and neurological status before primary surgery, maximum diameter, eloquent location, and bi-hemispheric extension of the tumor, EOR and residual lesion volume, histological type of the neoplasm, and presence of *IDH1/IDH2* mutations and 1p/19q co-deletion [7, 13, 27–29]. As was demonstrated in the present study, recurrence of LGG by itself also negatively influences the outcome. Among patients in the study group, median PFS and actuarial 10-year OS rate were 3.3 years and 56%, respectively, which is much worse than in the entire cohort of 227 consecutive cases of LGG operated on in our clinic within the same time span (median PFS, 12.0 years; actuarial 10-year OS rate, 80.1%; data not shown). Moreover, individual recurrence characteristics have statistically significant impact on prognosis. Early onset, fast radiological progression, and non-local site of relapsing tumor, each has negatively influenced OS of our patients. In addition, these unfavorable characteristics were significantly associated with malignant transformation of the neoplasm during follow-up.

Current WHO classification of CNS tumors [20] presumes assessment of *IDH1/IDH2* mutational status and 1p/19q co-deletion for definitive diagnosis of DA and OD. Both *IDH1/IDH2* mutations and 1p/19q co-deletion in gliomas carry favorable prognostic and predictive values and are associated with prolonged survival of patients [14, 15, 21, 29, 30]. According to our data, these molecular alterations may be also considered as one of the main determinants of recurrence characteristics after resection of LGG. As has been shown herein, *IDH1*-mutant tumors significantly more often demonstrate non-early onset and slow progressing recurrences, whereas 1p/19q co-deletion has been associated with non-early onset of relapse and its regional or marginal location. Thus, it may be hypothesized that realization of the positive prognostic impact of *IDH1/IDH2* mutations and 1p/19q co-deletion may be in part related to more favorable characteristics of relapse at the time of its development.

Presented series includes 16 cases (20%) of *IDH* wild-type DA (*IDH1*^R132H immunonegative), which, according to the updated WHO classification of CNS tumors (2016) [20], are considered as separate provisional pathological entity. These neoplasms comprise 7–30% of LGG, and usually do not display *TP53* mutation and 1p/19q co-deletion as well, thus designated as "triple-negative" gliomas [15]. Such molecular fingerprint is frequently considered to be associated with unfavorable clinical course and dismal prognosis. Nevertheless, presence of wild-type *IDH* in DA may not be invariably linked to poor outcome, unless these tumors carry other glioblastoma-like genetic alterations, e.g., activating mutation or high-level amplification of *EGFR*, gain of chromosome 7, loss of chromosome 10, activating mutation of *TERT* promoter, etc.[15, 31]. In fact, based on DNA methylation profiling, *IDH* wild-type astrocytomas of WHO grade II and III additionally carrying aforementioned genetic

Table 3 Comparative analysis of tumor recurrence characteristics in 3 molecularly defined groups of tumors with regard to extent of resection

Molecularly defined groups of tumors (N = 73[a])	Characteristics of tumor recurrence								
	Time of onset			Speed of radiological progression[b]			Location		
	Early	Non-early	P-value	Fast	Slow	P-value	Local	Non-local	P-value
Group I: oligodendrogliomas ($IDH1^{R132H}$ immuno-positive, 1p/19 co-deleted; N = 28)			0.8493			0.2007			NC
EOR ≥ 90% (N = 20)	2 (7%)	18 (64%)		5 (18%)	15 (54%)		20 (71%)	0 (0%)	
EOR < 90% (N = 8)	1 (4%)	7 (25%)		4 (14%)	4 (14%)		8 (29%)	0 (0%)	
Group II: $IDH1$-mutant diffuse astrocytomas ($IDH1^{R132H}$ immunopositive, 1p/19 non-codeleted; N = 32)			0.5929			**0.0006**			**0.0107**
EOR ≥ 90% (N = 25)	8 (25%)	17 (53%)		4 (13%)	20 (65%)		22 (69%)	3 (9%)	
EOR < 90% (N = 7)	3 (9%)	4 (13%)		6 (19%)	1 (3%)		3 (9%)	4 (13%)	
Group III: IDH wild-type diffuse astrocytomas ($IDH1^{R132H}$ immunonegative, 1p/19 non-codeleted; N = 13)			**0.0483**			0.1348			0.9056
EOR ≥ 90% (N = 7)	2 (15%)	5 (38%)		3 (23%)	4 (31%)		6 (46%)	1 (8%)	
EOR < 90% (N = 6)	5 (38%)	1 (8%)		5 (38%)	1 (8%)		5 (38%)	1 (8%)	

EOR extent of resection, *NC* not calculated, bold, statistically significant values

[a]Without 8 cases with unknown $IDH1^{R132H}$ mutational status or 1p/19q status

[b]In 2 cases this characteristic could not be assessed because of lack of images

features have been shown to cluster tightly with *IDH* wild-type glioblastomas [31]. Therefore, as suggested by the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW), identification of such molecular abnormalities in *IDH* wild-type LGG should be considered as a possible sign of highly aggressive biological behavior and allows for their designation as WHO grade IV tumors [31]. If additional clinicopathological studies validate this expert opinion based recommendation, it may be considered for inclusion into standard diagnostic criteria and histopathological grading scheme of the next edition of the WHO classification of CNS tumors. Optimal treatment strategies of *IDH* wild-type DA should be determined as well. An important finding of our study is that their aggressive resection may carry positive impact on prognosis and leads to similar recurrence characteristics as observed in *IDH1*-mutant DA and OD.

In cases of LGG, EOR ≥ 90% is associated with prolongation of both PFS and OS, reduced rates of malignant transformation, and better seizure control [9, 21, 26, 32]. Our data have shown that aggressive surgery may also result in more favorable characteristics of tumor relapse at the time of its development. It was demonstrated both in the entire cohort of patients, and in individual molecularly defined tumor types: EOR ≥ 90% led to reduced proportion of early recurrences in *IDH* wild-type DA, and was associated with more frequent appearance of slow progressing and local relapses of *IDH1*-mutant DA. In contrast, postoperative chemotherapy, which is currently considered as an important adjunct

for treatment of LGG [33, 34], did not show any impact on the investigated characteristics of recurrence. Moreover, FRT was associated with more frequent fast progressing and distantly located relapses. These findings may have several explanations. First, in our practice adjuvant therapy is usually administered if EOR of LGG is < 90% or there are some other "high-risk" factors, thus focal FRT might simply carry limited efficacy on tumor control in such cases. Second, irradiation might indeed improve local tumor control, but was unable to provide it in distant areas of the brain. Third, FRT might result in malignant transformation of LGG, which in turn led to faster tumor growth and dissemination. Further studies are definitely needed to clarify this issue.

The RTOG 9802 study included 111 adult patients (aged from 18 to 39 years) with supratentorial LGG after neurosurgeon-determined aggressive resection (EOR > 90%) into the observation arm [16, 34]. In this cohort, in 82% of cases the recurrence was located within 2 cm of the resection cavity [16]. Such proportion of local relapses seems comparable with results of EORTC 22845 trial; in its early FRT arm in-field recurrences were noted in 90.4% of cases [7]. In the present series local recurrences were noted in 88% of patients in the entire study group, and in 93% of cases with EOR ≥ 90%. In the latter cohort postoperative FRT was significantly associated with early onset, fast radiological progression, and non-local site of relapse. Such finding justifies our current strategy to omit early adjuvant therapy for LGG in cases with EOR ≥ 90% in favor of observational follow-up with regular MRI examinations [21].

Conclusions

Tumor recurrence patterns after surgical resection of LGG are characterized by significant variability and differ in distinct molecularly defined types of tumors. OD typically demonstrate late and local relapses, whereas DA usually recur earlier and relatively more often in distant locations. In particular, *IDH* wild-type DA are prone for early recurrence with fast radiological progression. Early onset, fast progression, and non-local site of relapsing tumor negatively influence OS of patients and are often associated with malignant transformation of LGG. Nevertheless, aggressive resection (EOR ≥ 90%) at the time of primary surgery may alleviate effects of molecularly defined tumor type on recurrence characteristics and result in their more favorable patterns, whereas administration of postoperative FRT may have opposite effects.

Compliance with ethical standards

Conflict of interest This study contains no conflict of interests.

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