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Overall survival prediction scale for patients with grade 4 brain astrocytoma

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ABSTRACT

Objective. To create a prognostic scale for overall survival in grade 4 astrocytomas based on molecular biological data.

Material and methods. After morphological confirmation of WHO grade 4 astrocytoma (2021 WHO classification criteria), 175 patients were classified as GBM (grade 4) without *IDH1* mutations; *IDH1* mutation was detected in 25 patients (12.5%; G4 astrocytoma). Molecular biological analysis of *IDH1* gene mutations and MGMT promoter methylation was performed in 194 (97%) patients.

Results. To study concomitant significance of *IDH1* mutation and MGMT promoter methylation in grade 4 gliomas, we created the *IDH1*/MGMT index(0 — *IDH1*+/MGMT+; 1 — *IDH1*/MGMT (+/–); 2 — *IDH1*-/MGMT-). This predictor was digitized in 194 patients who underwent molecular analysis. The most informative classification matrix according to overall survival was as follows: *IDH1*/MGMT index (OR=1.712; p=0.0004), REP (OR=1.971; p=0.0001), functional status before microsurgery at the lowest possible level (OR=1.797; p=0.001). Simple summation of numerical indicators for factors 1—3 in each patient allowed us to identify 5 prognostic classes: class 1 (0—1 points), class 2 (2 points), class 3 (3 points), class 4 (4 points), class 5 (5 points). Log-rank criterion for Kaplan—Meier survival curves revealed significant differences between classes (χ2=55.780; p<0.001). The median survival rates were 71.5, 42.3, 23.6, 17.4 and 8.1 months, respectively. Significant differences in survival were noted between almost all neighboring classes: classes 1—2 (χ2=3.21; p=0.073), classes 2—3 (χ2=5.77; p=0.016), classes 3—4 (χ2=6.03; p=0.014), classes 4—5 (χ2=11.97; p=0.0005). In "classes 1—3" in prognostic scale, median overall survival was 44.98 months (n=53; 95% CI: 20.5—69.4) for 3 Gy fractionation regimen and only 23.23 months (n=78; 95% CI: 17.3—29.1; χ2=9.28; p=0.002) for 2 Gy regimen. There were other results for classes 4—5. Median overall survival for 3 and 2 Gy fractionation regimens was low: 17.41 (n=28; 95% CI: 13.8—21.0) and 15.83 months (n=41; 95% CI: 11.7—20.0; –2=0.59; p=0.442), respectively.

Conclusion. The new prognostic scale for overall survival, based on molecular data, allows not only to predict further course of disease, but also to recommend irradiation 3 Gy for patients in classes 1—3 as an alternative to radiotherapy.

Keywords: *glioblastoma, radiotherapy, prognostic scale.*

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Abbreviations

GB — glioblastoma
IDH1 — isocitrate dehydrogenase 1
MGMT — O^6-methylguanine DNA methyltransferase
EOR — extent of resection
REP — rapid early progression
NonREP — no rapid early progression
TMZ — temozolomide
GTV — gross tumor volume
CTV — clinical target volume
PTV — planning target volume
RPA — recursive partitioning analysis

Introduction

Advances of molecular genetics inspired changes in WHO classification of CNS tumors and creation of the 5th version of this classification (2021) [1]. According to this classification, molecular testing has become mandatory for accurate diagnosis. IDH gene mutations are a key diagnostic feature for diffuse gliomas grade II—IV in adults. According to the 5th version, the category "diffuse gliomas in adults" is simplified to three main types:

— astrocytoma with IDH gene mutations (grades II—IV);
— oligodendroglioma with IDH gene mutations and 1p/19q codeletion (grades II—III);
— GB without IDH gene mutations.

GB with IDH gene mutations was excluded from classification. These neoplasms are now designated as "astrocytoma with IDH gene mutations grade IV" [1]. Any diffuse astrocytoma without IDH1/IDH2 gene mutations should be recognized as GB [1, 2]. In addition to molecular data, histological diagnosis and grade are key factors in determining treatment strategy and prognosis [1—3].

The purpose of the study was to develop a prognostic scale for overall survival in grade IV gliomas based on molecular data.

Material and methods

Two hundred patients with grade IV gliomas were followed-up at the National Research Medical Center of Radiology. The main sample consisted of 138 patients. Pairwise selection strategy assumes a known parameter that can significantly influence experimental outcome. In our study, such a parameter was radiotherapy fractionation method. Since 2015, patients younger 50 years have undergone radiotherapy with alternating fractionation (2 and 3 Gy). The first patient was assigned a dose of 3 Gy, the next patient — 2 Gy (pairwise selection strategy). The same approach was used for older patients (⩾ 50 years) [4, 5]. We added patients treated after the end of recruitment to study groups (death or follow-up after start of primary treatment > 24 months). After morphological confirmation of grade IV glioma (2021 WHO classification criteria), 175 patients were classified as GB (grade IV) without IDH1 mutations, and IDH1-mutant astrocytoma was detected in 25 patients. Molecular testing with analysis of IDH1 mutations and MGMT promoter methylation was performed in 194 (97%) patients.

Total resection (no MR signs of residual tumor after surgery) was performed in 32.5% (EOR: 100%; n=65), subtotal resection — 56.5% (EOR: 70—99%; n=113). EOR 1—69% was observed in 22 (11.0%) patients.

REP was diagnosed in 84 (42.0%) patients, nonREP — in 116 (58.0%) patients. REP implied a new area of contrast enhancement and/or enlargement of appropriate focus by more than 25% according to MRI data [4, 5].

Radiotherapy was performed only on linear accelerators. The study included patients Karnofsky score ⩾70% before radiotherapy. Patients with lower functional status were scheduled for early chemotherapy at the first stage. Early chemotherapy (1—6 courses with TMZ) between microsurgery and radiotherapy [6] was performed in 67 (33.5%) patients due to low functional status after microsurgery (Karnofsky score<70%) or impossible radiotherapy in the current year. Our previous trial showed that early chemotherapy followed by radiotherapy did not worsen prognosis compared to standard treatment course (surgery+radiotherapy) for grade IV gliomas [6]. After improvement of functional status, radiotherapy was administered in scheduled volume for all patients. Among 200 patients, 142 (71.0%) ones underwent radiotherapy under TMZ 75 mg/m^2.

Mean period between microsurgery and radiotherapy was 6.4 weeks (95% CI 6.0—7.1).

Total dose. In the 2 Gy group (n=119), 105 (88.2%) patients completed the scheduled dose (30—32 fractions). Other ones did not complete radiotherapy for various reasons. In the 3 Gy group (n=81), 79 (97.5%) patients completed the full course of radiotherapy (18—19 fractions).

Scheduled irradiation volume for 2 fractionation options was determined as follows:

- GTV necessarily included postoperative cystic cavity and contrast-enhanced tumor mass (if present);
- CTV included GTV+2 cm; edema zone was within CTV boundaries. No additional margins were made to form PTV (CTV=PTV);
- mean dose for 2 fractionation options was as close as possible to prescribed dose (2/3 Gy). Mean dose for regimen with the prescribed dose 2 Gy was 2.014 Gy (95% CI: 2.01—2.02), for regimen with the prescribed dose 3 Gy — 3.028 Gy (95% CI: 3.02—3.04).
- 90% of the prescribed dose (1.8 Gy for 2 Gy regimen and 2.7 Gy for 3 Gy regimen) were required to cover > 95% CTV; median coverage for two fractionation options was 99.78% (95% CI: 99.6—99.9).

Standard first-line therapy with TMZ 200 mg/m^2 (the first course at a dose of 150 mg/m^2) was administered to 170 (85.0%) patients. In 7 (3.5%) patients, it was prescribed due to complications, in 13 (6.5%) cases — due to growth after previous TMZ therapy. Nine (4.5%) patients died from previous treatment, and one (0.5%) patient did not receive first-line therapy due to concurrent cancer. TMZ chemotherapy program with 6—12 courses was successfully completed in 83 (41.5%) patients. Most ones had continued growth under adjuvant TMZ therapy.

Bevacizumab 5—10 mg/kg on days 1 and 15 (+/— irinotecan/lomustine) as second-line therapy after primary progression (n=152) was administered to 104 out of 140 patients (76.0%). Other patients did not undergo second-line therapy for various reasons (no primary progression (24 patients, 12.0%) or refusal of specific treatment due to low performance status).

There were no differences between groups with two fractionation regimens in age (p=0.203) or primary performance status (p=0.853). The groups were similar regarding EOR (p=0.079), REP (p=0.767), TMZ alongside radiotherapy (p=0.877), adjuvant TMZ (p=0.095), second-line therapy with bevacizumab (p=0.248), IDH1 (p=0.689) and MGMT status (p=0.279). Only early chemotherapy was used somewhat more frequently with 3 Gy fractionation regimen (p=0.036).

Our local statistical database integrates approximately 200 different parametric and nonparametric factors for each patient. We analyzed results using IBM SPSS Statistics (version 27.0). Differences between Kaplan—Meier curves were determined using the log-rank test (χ2). Prognostic factors were significant at p<0.05. Multivariate analysis was performed using proportional hazard

Table 1. **IDH1/MGMT scoring**

Predictor	Number of patients	Value	Score	Median of overall survival, months
IDH/MGMT index	13	*IDH1+/MGMT+*	0	71.49
	75	*IDH1/MGMT (+/–)*	1	33.12
	106	*IDH1–/MGMT–*	2	18.96

Table 2. **Overall survival prognosis scale for grade IV gliomas**

Predictors	Value	Score
REP	NonREP	0
	REP	1
IDH/MGMT index	*IDH1+/MGMT+*	0
	IDH1/MGMT (+/–)	1
	IDH1–/MGMT–	2
Karnofsky score	⩾80	0
	60—70	1
	⩽50	2

model (Cox regression). It included predictors that were significant in univariate analysis ($p<0.05$), as well as other parametric and nonparametric variables. Analysis implied stepwise inclusion/exclusion. In this model, Exp(B) reflects odds ratio change (OR or hazards ratio, HR) with significance at $p<0.05$.

Results

A total of 152 (76.0%) patients died, and 138 (69.0%) ones died from glioma progression. The follow-up for survivors exceeds 24 months.

To study simultaneous significance of IDH1 mutations and MGMT promoter methylation in grade IV gliomas, we developed a metric called the IDH1/MGMT index **(Table 1)**.

According to univariate analysis, IDH1/MGMT index ($\chi2=20.56$; $p=0.00003$) was more significant regarding overall survival than IDH1 mutation ($\chi2=14.47$; $p=0.00014$) and MGMT promoter methylation ($\chi2=8.90$; $p=0.003$). Multivariate analysis confirmed this trend: IDH1/MGMT index (OR=1.592; $p=0.008$) versus IDH1 (OR=0.510; $p=0.079$) and IDH1/MGMT index (OR=3.120; $p=0.00058$) versus MGMT methylation (OR=1.959; $p=0.079$).

The overall survival prognosis scale was based on treatment outcomes of 194 patients with grade IV gliomas who underwent molecular testing. The most informative classification matrix was as follows: IDH1/MGMT index (OR=1.712; $p=0.0004$), REP (OR=1.971; $p=0.0001$) and low preoperative Karnofsky score (OR=1.797; $p=0.001$). Age (< 50 years and ⩾50 years) was a less significant factor (OR=1.578; $p=0.016$) and not included in final model. The most informative predictors were scored **(Table 2)**.

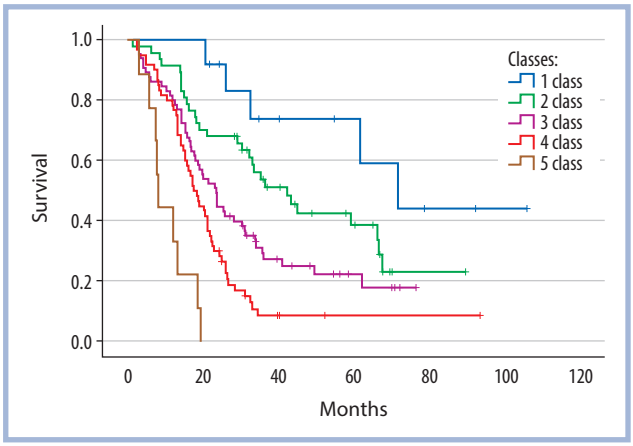

Fig. 1. **Kaplan—Meier overall survival curves based on prognostic criteria.**

Table 3. **Median overall survival in different classes**

Scale	Number of patients	Median, months	95% CI
Class 1	13	71.49	47.5—95.5
Class 2	47	42.32	29.7—54.9
Class 3	65	23.56	19.0—28.1
Class 4	60	17.41	14.5—20.3
Class 5	9	8.05	7.0—9.1

Summarizing numerical scores identified 5 prognostic classes: class 1 (0—1 point), class 2 (2 points), class 3 (3 points), class 4 (4 points) and class 5 (5 points). Class 1 combines scores 0—1 due to small number of patients with score 0 ($n=3$). Kaplan—Meier survival curves revealed significant differences between classes ($\chi2=55.780$; $p<0.001$) **(Fig. 1, Table 3)**.

With the exception of classes 1—2, we found significant differences in survival between all adjacent classes: classes 1—2 ($\chi2=3.21$; $p=0.073$), classes 2—3 ($\chi2=5.77$; $p=0.016$), classes 3—4 ($\chi2=6.03$; $p=0.014$), classes 4—5 ($\chi2=11.97$; $p=0.0005$).

Practical significance of overall survival prognosis scale

In classes 1—3, median overall survival for 3 Gy fractionation was 44.98 months ($n=53$; 95% CI: 20.5—69.4), for 2 Gy fractionation — 23.23 months ($n=78$; 95% CI: 17.3—29.1; $\chi2=9.28$; $p=0.002$) **(Fig. 2)**.

There were no significant differences in overall survival between two fractionation regimens in individual classes. However, the trend towards better outcomes for hypofractionated regimen remains quite significant. Median survival for the prescribed dose 3 and 2 Gy in class 1 was not reached (median survival 85.8 and 50.3 months, respectively; $\chi 2=2.51$; $p=0.113$), for class 2 — 67.5 and 33.1 months ($\chi 2=3.85$; $p=0.05$), for class 3 — 30.3 and 18.6 months ($\chi 2=2.79$; $p=0.095$).

We obtained other results for classes 4—5. Median overall survival for 3- and 2-Gy fractionation was low: 17.41 ($n=28$; 95% CI: 13.8—21.0) and 15.83 months ($n=41$; 95% CI: 11.7—20.0; $\chi 2=0.59$; $p=0.442$), respectively **(Fig. 3)**.

Median survival with the prescribed dose 3 and 2 Gy for class 4 was 17.4 and 17.2 months, respectively ($\chi 2=1.58$; $p=0.209$), for class 5 — 3.0 and 8.0 months, respectively (mean survival 11.1 and 10.4 months, respectively; $\chi 2=0.65$; $p=0.421$).

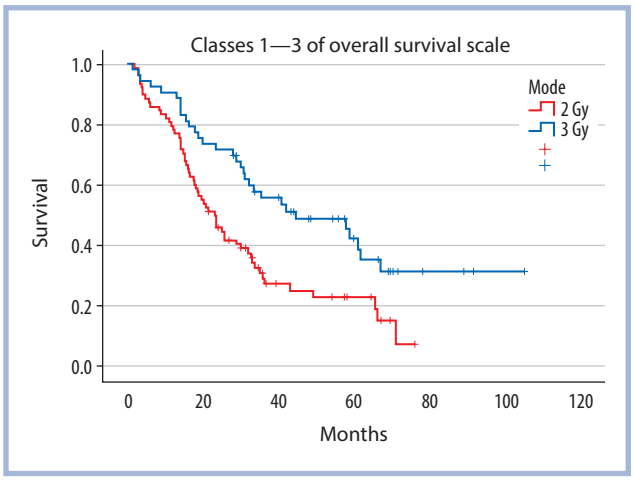

Fig. 2. **Survival curves for 3 and 2 Gy fractionation regimens in prognostic classes 1—3.**

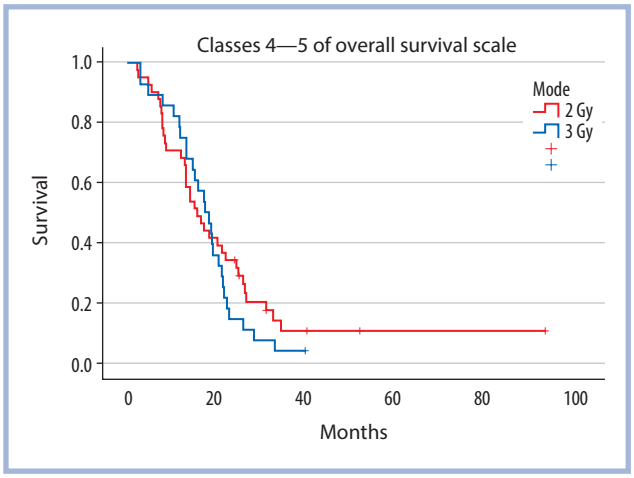

Fig. 3. **Survival curves for 3 and 2 Gy fractionation regimens in prognostic classes 4—5.**

Multivariate analysis for optimal fractionation.

The Cox survival regression model identified some significant factors ($p<0.001$) for overall survival in grade IV gliomas **(Table 4)**.

Taking into account four significant predictors, we analyzed the role of two fractionation regimens depending on whether patients belonged to prognostic classes 1—3 and classes 4—5. Diametrically opposed results were obtained **(Fig. 4)**.

For patients in classes 1—3, hypofractionated regimen had significant advantages over standard radiother-

Table 4. **Predictors of overall survival in grade IV gliomas**

Predictors of overall survival	OR	*p*
Isoeffective dose<59.5⩾ Gy [7]	0.178	<0.001
REP	1.636	0.004
Second-line therapy with bevacizumab	0.303	<0.001
Time to primary progression	0.898	<0.001

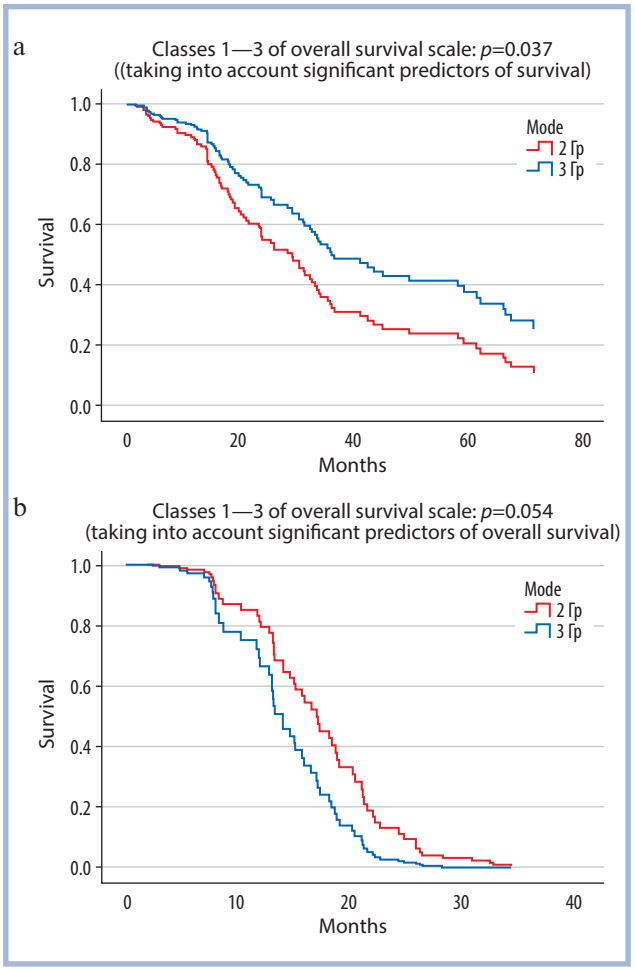

Fig. 4. **Survival curves for 3- and 2-Gy fractionation regimens (taking into account four significant predictors of overall survival) depending on whether patients belonged to classes 1—3 (a) or classes 4—5 (b).**

apy (p=0.037), while predictors of isoeffective dose with alpha/beta ratio 7.5 (<59.5⩾Gy), second-line therapy with bevacizumab and time to primary progression were significant at p<0.001.

For classes 4—5, there is a clear trend towards better survival for standard radiotherapy (p=0.054). Isoeffective dose with alpha/beta ratio 7.5 (<59.5⩾Gy), second-line therapy with bevacizumab and time to primary progression remained significant (p<0.001).

Discussion

The RPA classification, published over 30 years ago and based on patient age, tumor tissue morphology (glioblastoma, anaplastic astrocytoma), mental and functional status, extent of resection and some other factors [8], has become a significant contribution to further research of gliomas. The randomized trial EORTC 26981/22981 demonstrated that RPA classes retain their prognostic value in patients receiving radiotherapy with or without TMZ for GB, particularly for classes III and IV. Survival difference in the RT/TMZ group was borderline for class V (p=0.054) [9].

A simplified version of RPA classification for GB did not demonstrate higher efficacy. However, it is easier to use because it includes only four variables: age, performance status, extent of resection, and functional status. Median survival after updating the GB patient database for classes III, IV and V+VI was 17.1, 11.2, and 7.5 months, respectively (p<0.0001). It is emphasized that simplified original RPA model combining classes V and VI will be used in future RTOG studies in GB. Moreover, research of MGMT methylation status and R132H mutation in IDH1 gene may further facilitate assessment of patient risk at diagnosis and subsequently improve individualized and targeted treatment. Update of RPA classification to include new markers once their role is established was proposed [10]. In recent years, genetic markers of GB and their role in predicting outcomes have been actively studied.

No methylation was associated with worse survival according to univariate (p<0.001) and multivariate (p<0.001) analysis of 680 GB patients (330 MGMT+, 264 MGMT–, MGMT undetectable in 86) [11].

Combination of methylated MGMT+promoter and mutation in IDH1+gene is associated with significantly longer survival. Biological factors affecting long-term survival were studied in 100 patients with GB who underwent chemo- and radiotherapy. The Cox proportional hazards model identified several independent prognostic factors: MGMT promoter methylation (p<0.0001) and IDH1 mutation (p=0.023). In the MGMT+/IDH1+subgroup, median overall survival was 66.8 months, in MGMT+/IDH1– — 15.5 months, in MGMT–/IDH1– — only 11.1 months (p=0.000) [1].

In the study dated 2022 [3], median overall survival among 273 patients with wild-type IDH GB and MGMT methylation was 25.7 months (116 patients), without methylation — 14.0 months (125 patients; p=0.009).

The new overall survival prognosis scale presented in this article is partially based on molecular data. This grading system allows for prediction of subsequent course of disease (p<0.001). According to this scale, hypofractionated regimen (dose 3 Gy) is recommended for classes 1—3 (p=0.002).

We may further validate new data in prospective study on a “test” sample to assess significance of this tool.

Conclusion

Molecular testing for IDH1 mutations and MGMT promoter methylation immediately after microsurgery for grade IV gliomas is indicated not only for correct diagnosis according to 2021 WHO classification, but also for early prognosis of disease and selection of optimal fractionation for radiotherapy.

Our data demonstrate feasibility of hypofractionated radiotherapy for grade IV gliomas. However, non-standard radiotherapy options with sufficiently high isoeffective doses can currently be used in only scientific protocols or with the patient’s informed consent.

Author contribution:
Concept and design of the study — Datsenko P.V., Chuguev A.S.
Collection and analysis of data — Datsenko P.V., Chuguev A.S., Gerasimov V.A.
Statistical analysis — Chuguev A.S., Datsenko P.V.
Writing — Chuguev A.S., Datsenko P.V.
Editing — Kaprin A.D.

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