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Prognostic factors to predict postoperative survival in patients with recurrent glioblastoma

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ABSTRACT

Background: There are no generally accepted criteria for selecting patients with recurrent glioblastoma for surgery. This retrospective study in a Danish population-based cohort aimed to identify prognostic factors affecting postoperative survival after repeated surgery for recurrent glioblastoma and to test if the preoperative New Scale for Recurrent Glioblastoma Surgery (NSGS) developed by Park CK et al could assist in the selection of patients for repeat glioblastoma surgery.

Methods: Clinical data from 66 patients with recurrent glioblastoma and repeated surgery were analyzed. Kaplan–Meier plots were produced to illustrate survival in each of the three NSGS prognostic groups, and Cox proportional hazard regression was used to identify prognostic variables. Multivariable analysis was used to identify differences in survival in the three prognostic groups.

Results: Six variables significantly affected postoperative survival: preoperative Karnofsky Performance Status (KPS) < 70 ($p = 0.002$), decreased KPS after second surgery ($p = 0.012$), ependymal involvement ($p = 0.002$), tumor volume $\geqq 50$ cm^3 ($p = 0.021$), age ($p = 0.033$) and Ki-67 ($p = 0.005$). Retrospective application of the criteria previously published by Park CK et al showed that median postoperative survival for the three prognostic groups was 390 days (0 points), 279 days (1 point), and 80 days (2 points), respectively.

Conclusion: Several prognostic variables to predict postoperative survival in patients with recurrent glioblastoma were identified and should be considered when selecting patient for repeat surgery. The NSGS scoring system was useful as there were significant differences in postoperative survival between its three prognostic groups.

1. Introduction

Glioblastoma (GBM) is the most common malignant primary brain tumor and has a poor prognosis despite optimal neurosurgical and oncological treatment.[1] The median overall survival for all glioblastoma patients in Denmark from 2009 to 2012 was 11.2 months whereas patients who underwent full postsurgical oncological treatment had a median overall survival of 16.1 months.[2] The initial treatment of glioblastoma includes maximal safe surgical resection followed by concomitant radio-chemotherapy with concurrent and adjuvant temozolmide.[1] Recurrence is inevitable, and most patients experience recurrence within 6–9 months after initial treatment.[3]

Repeat surgery may improve survival, tumor-related neurologic symptoms, and quality of life, but it is also associated with potential risks and side effects.[4–6] Repeat surgery is avoided if the patient has poor performance status or if the tumor is no longer suitable for surgical resection.

There are no generally accepted guidelines regarding which patients with recurrent glioblastoma will benefit from repeat surgery. It is generally accepted that factors such as performance status, tumor location and size, time from initial surgery to progression, and the possibility of other treatments all influence the outcome and are important to consider when evaluating whether a patient should be offered repeat surgery.[7–10]

Park JK et al[10] were the first to devise a preoperative scale (National

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Abbreviations

ASA score = The American Society of Anaesthesiologists Physical Status Classification System
CI = Confidence interval
GBM = Glioblastoma
HR = Hazard ratio
ICD10 = International Classification of Diseases
IDH1 = Isocitrate dehydrogenase-1
Ki-67 = Proliferations index
KPS = Karnofsky Performance Status
MGMT = O6-methylguanine-DNA methyltransferase
MRI = Magnetic resonance imaging
NSGS = New Scale for Recurrent Glioblastoma Surgery
RANO criteria = Response assessment in neuro-oncology criteria
WHO = World Health Organization

Institutes of Health [NIH] Recurrent GBM Scale) to predict survival after surgery for recurrent glioblastoma. Tumor involvement of eloquent/-critical brain regions, Karnofsky performance status (KPS), and tumor volume were found to have a significant influence on survival after repeated surgery and were therefore included in the scale.[10] The scoring system was later updated with a more practical scoring system, the New Scale for Recurrent Glioblastoma Surgery (NSGS).[9]

Using a Danish historic prospective cohort, the purposes of the present study were 1) to investigate if preoperative NSGS[9] could be used to anticipate the outcome of repeat surgery for glioblastoma in a Danish population-based cohort, and 2) to investigate additional prognostic variables affecting the postoperative survival of glioblastoma patients in our clinical setting.

2. Patients and methods

Using the diagnostic code (ICD10) DC71 together with the cancer code A + ZACA4 and surgical code KAAB, we retrospectively collected clinical data from 66 patients who underwent initial and repeat surgery at Department of Neurosurgery, Odense University Hospital in 2015–2019. The patients were classified according to the WHO CNS5 criteria.[11] All patients had histologically confirmed recurrent glioblastoma (IDH wildtype), and had undergone at least two craniotomies and tumor resections.

Recurrence was defined as reappearance of or enlarged contrast-enhancement on magnetic resonance imaging (MRI) and was assessed using the Response assessment in neuro-oncology criteria (RANO criteria) for high-grade gliomas.[12]

Patients were excluded if they did not have a histologically verified glioblastoma or did not have follow-up MRI scans. If patients had undergone more than two surgeries, only data from the initial surgery and the second surgery were included in the study. After surgery, patients received radiotherapy with concomitant and adjuvant temozolomide. Patients who had not tolerated or had declined adjuvant treatment were omitted from the study. One patient had received nivolumab instead of temozolomide. After the initial surgery, patients were followed with standard brain tumor MRI every three months, or earlier if clinical deterioration was observed. At recurrence, all patients underwent maximal safe surgical resection to prolong survival or reduce neurological symptoms, and an early postoperative MRI within 72 hours was performed to determine the extent of resection. After repeat surgery, patients received further postoperative chemotherapy.

Survival time was measured in days from the date of the second surgery to the date of the patient's death. All patients were observed until their date of death or 03.11.2020.

The project was approved by the Danish Patient Safety Authority (31-1521-172) and the Data Protection Agency (20–7126).

2.1. Prognostic variables

Data available at time of recurrence were collected from medical records (Table 1). Demographic variables included age and gender. Clinical variables included KPS at recurrence (dichotomized as ≧ 70 or < 70), dates of surgeries, presence of seizures and headache at recurrence, cognitive or neurological functional deficits at recurrence, and number of days from initial surgery to recurrent surgery. Treatment variables included radiation with concomitant and adjuvant chemotherapy after initial surgery, chemotherapy after second surgery, and time between surgery and chemotherapy. Radiographic variables included hemisphere and lobe of tumor location, ependymal involvement of the tumor in the MRI at recurrence, tumor volume, and RANO

Table 1
Demographic, clinical, radiographic and treatment characteristics of the study cohort.

Characteristics	Median	Range
Age, years	62	37–78
	n	%
Female sex	31	46.9
Performance status, KPS ≧ 70	58	87.9
KPS unchanged	54	81.82
KPS increased	1	16.67
KPS decreased	11	1.52
ASA score <2	44	66.7
Adjuvant chemotherapy	62	93.9
Temozolomide	27	40.9
Avastin	3	4.5
Avastin + Irinotecan	26	39.4
CCNU (Lomustine)	6	9.1
	Median	Range
Time between initial surgery and repeat surgery, days	399	42–1933
Time between initial surgery and chemotherapy, days	29.5	15–105
Time between repeat surgery and chemotherapy, days	28	10–95
Number of patients with	n	%
Neurological function deficient	38	57.6
Seizures	11	16.7
Headache	23	34.9
Cognitive deficiencies	13	19.7
Tumor characteristics	Median	Range
Ki67	50%	10%–100%
	n	%
MGMT methylated	31	46.9
RANO criteria at initial surgery		
No residual tumor	14	21.2
Not measurable	32	48.5
Measurable	19	28.8
Not known	1	1.5
RANO criteria at repeat surgery		
No residual tumor	6	9.1
Not measurable	28	42.4
Measurable	32	48.5
Left side tumor location	34	51.5
Recurrence in the previous resection cavity wall	49	72.1
Predominant lobe of tumor location		
Frontal	19	28.8
Temporal	15	22.7
Parietal	14	21.2
Occipital	8	12.1
Spanning several regions	10	15.2
Bilateral tumor	2	3
Ependymal involvement	35	53
Tumor volume ≧ 50 cm3	8	12.1
EOR at recurrence ≧ 95%	35	53

Abbreviations: KPS, Karnofsky performance status. RANO, Response assessment in neuro-oncology. EOR, Extent of resection.

criteria both after initial surgery and repeat surgery.[12] Tumor volume was approximated by calculating (A x B x C)/2, where A, B, and C were perpendicular to each other at the greatest diameter. Histomolecular status from first surgery included IDH1 status (conforming IDH wild-type), proliferation index (Ki-67), and MGMT promotor methylation status (methylated or non-methylated).[13] MGMT status was determined using the pyrosequencing kit from Qiagen (Hilden, Germany) as previously described. Threshold was set to 10% methylation on one of the four sites measured in the analysis.[14]

2.2. Statistical analysis

Based on the NSGS scoring system, patients were divided into three prognostic groups (score range 0–2 points; 1 point for KPS <70 and 0 for KPS ≧ 70; 1 point for ependymal involvement and 0 for no ependymal involvement),[9] and the scores were then correlated with postoperative survival time. Kaplan–Meier plots were used to illustrate postoperative survival in patients with recurrent glioblastoma in the three NSGS prognostic groups.[9] Variables that were not included in the NSGS were examined separately for their ability to predict outcome. To determine potential prognostic factors, we first tested the clinical data in a univariate analysis of postoperative survival and then applied Cox proportional hazard regression. Only significant variables ($p < 0.05$) in the univariate analysis were included in the multivariable analysis. Statistically insignificant variables were excluded from further investigation (Appendix 1).

Statistical analysis of the three NSGS prognostic groups was performed using the Breslow test (multivariable analysis).[9] Pairwise comparisons of survival in the three prognostic groups were performed. Results were regarded as statistically significant if $p < 0.05$. Statistical analyses were performed using STATA/IC (version 16.1).

3. Results

Of the 100 patients initially identified, 66 patients were included for analysis (Fig. 1). Their baseline demographic, clinical, treatment, and radiographic characteristics are summarized in Table 1. The median survival after second surgery among all patients was 335 days. 49 (72.1%) patients had recurrence in the previous resection cavity wall, and the median time between initial surgery and repeated surgery was 399 days (range, 42–1933 days). The median time between surgery and chemotherapy was similar after initial and repeat surgery (29.5 vs 28 days).

3.1. Prognostic factors for postoperative survival

Table 2 shows the demographic, clinical, treatment and radiographic factors that were found to be significantly ($p < 0.05$) related to postoperative survival. Statistically insignificant variables are shown in Appendix 1. Variables with more than two possible values (e.g., KPS, tumor volume, ASA score) were dichotomized using cut-offs based on previous literature and clinical experience.[8–10,15] Although age and time between initial and repeat surgery were not significant in the univariate analysis, they were included in the multivariable analysis as a potential confounders. Six variables remained significant in the multivariable analysis: KPS <70 before repeated surgery ($p = 0.002$), decreased KPS after second surgery ($p = 0.012$), tumors with ependymal involvement ($p = 0.002$), tumor volume ≧ 50 cm^3 ($p = 0.021$ and age ($p = 0.033$) were all associated with decreased median survival. High Ki-67 had a negative effect on overall survival ($p = 0.005$) although the confidence

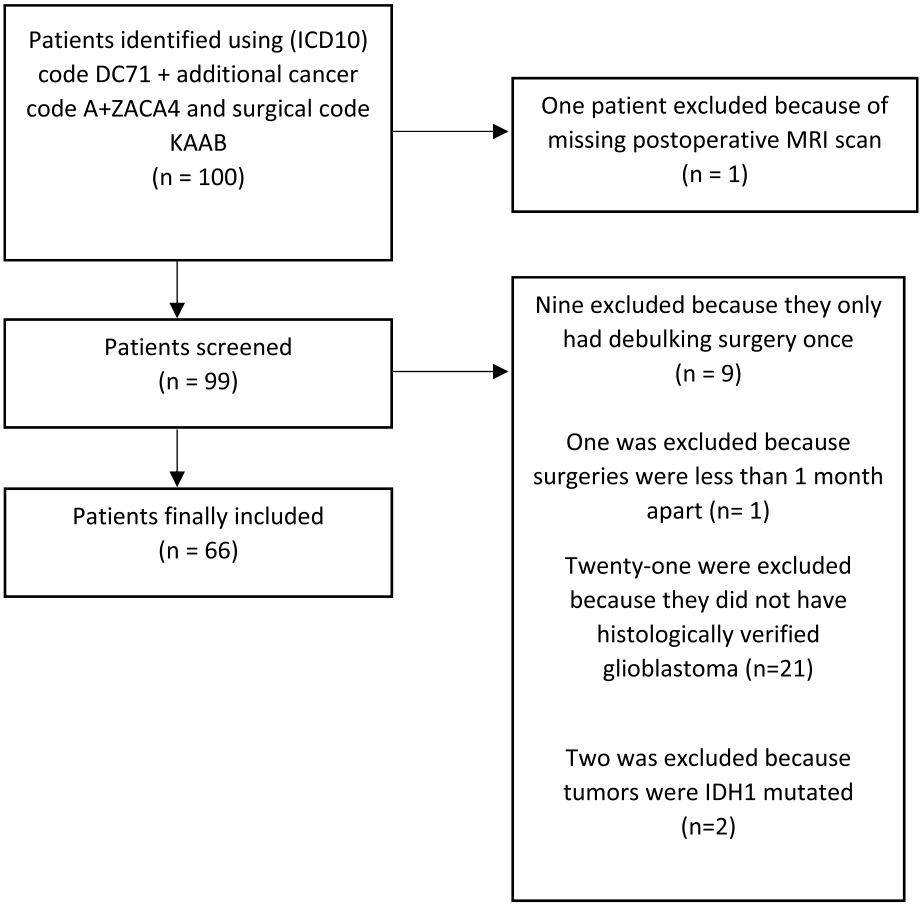

Fig. 1. Patient selection and exclusion criteria.

Table 2
Univariate analysis and multivariable Cox Proportional-Hazard results of prognostic factors.

Variables	Median survival (days)		Univariate analysis, *p* value	HR *[95% CI]*	Multivariate analysis, *p* value	Multivariate analysis, HR [95% CI]
	Yes	No				
KPS <70	122	347	0.004	3.10 [1.44–6.66]	0.002*	15.25 [2.68–86.76]
Decreased KPS after second surgery	140	351.5	0.003	2.90 [1.42–5.94]	0.012*	4.47 [1.39–14.29]
Time between initial surgery and repeat surgery	N/A		0.086	0.99 [0.999–1.000]	0.069	0.99 [0.998–1.000]
Neurological functional deficient	260	390	0.022	1.84 [1.09–3.09]	0.998	0.99 [0.48–2.08]
Seizures	208	345	0.032	2.09 [1.06–4.09]	0.096	2.22 [0.87–5.65]
Cognitive deficiencies	213	354	0.033	2.04 [1.06–3.94]	0.989	1.01 [0.40–2.52]
Ependymal involvement	279	377	0.027	1.79 [1.07–3.01]	0.002*	3.19 [1.51–6.79]
Ki67	N/A		0.018	4.83 [1.31–17.79]	0.005*	9.96 [1.99–49.88]
Bilateral tumor	153.5	338.5	0.048	4.42 [1.01–19.31]	0.484	2.07 [0.27–15.87]
Adjuvant treatment	342.5	83.5	0.000	0.09 [0.03–0.31]	0.183	0.26 [0.04–1.87]
ASA ≧ 3	231	356.5	0.047	1.77 [1.01–3.11]	0.576	0.76 [0.34–1.83]
Tumor volume ≧ 50 cm3	123.5	351.5	0.000	4.47 [1.97–10.14]	0.021*	5.31 [1.28–22.03]
Age	N/A		0.995	1.00 [0.97–1.03]	0.033*	0.96 [0.93–0.99]

*Significant with $p < 0.05$.
Abbreviations: KPS, Karnofsky performance status. HR, Hazard Ratio. CI, Confidence interval. N/A, not applicable.

intervals were wide [1.99–49.88] (Table 2).

3.2. Validation of NSGS

According to the NSGS, 26 patients (39.4%) had 0 points and were assigned to a good prognostic group (median survival 390 days; 95% CI, 320–493 days); 37 patients (56.1%) had 1 point and were assigned to an intermediate prognostic group (median survival 279 days; 95% CI 189–349 days), and three patients (4.5%) had 2 points and were assigned to a poor prognostic group (median survival 80 days; 95% CI, 35–129 days) (Table 3).

This was confirmed in the survival analysis for the three groups (Fig. 2, Table 4). Patients in the good prognostic group had significantly longer survival than patients in the intermediate prognostic group (HR, 2.06; 95% CI, 1.19–3.55; $p = 0.009$) or in the poor prognostic group (HR, 18.31; 95% CI, 4.67–71.68; $p = 0.000$). Patients in the intermediate prognostic group also had significantly longer survival than patients in the poor prognostic group (HR, 8.89; 95% CI, 2.39–32.99; $p = 0.001$).

4. Discussion

Glioblastoma recurrence is inevitable but repeat surgery will be considered in some patients to prolong survival and reduce tumor-related symptoms. Surgery has potential risks and side effects, however, so detailed knowledge about prognostic factors is important. While previous studies have investigated such factors, they were conducted before the introduction of the Stupp regime, which has significantly altered the treatment of glioblastoma. New investigations into prognostic factors are therefore needed.

In this retrospective study of 66 patients who had undergone repeat surgery for recurrent glioblastoma, we found that KPS at recurrence, decreased KPS after second surgery, age, ependymal involvement at time of recurrence, tumor volume and Ki-67 had a significant effect on postoperative survival. Thus, KPS <70 before repeat surgery and tumor volume ≧ 50 cm^3 were associated with shorter median survival, while patients who experienced a decrease in KPS after repeated surgery also had significantly decreased median survival. Tumors with ependymal involvement were also associated with shorter median survival, as expected, and it may be necessary to consider more carefully whether these patients will benefit from repeat surgery.

High Ki-67 had a significant negative effect on overall survival. This is interesting as previous studies have shown no prognostic value of Ki-67 in patients with glioblastoma.[16,17] Although the confidence interval

Table 3
Prognostic groups as defined by NSGS ($n = 66$) from Park CK et al.

Prognostic groups	NSGS score	Number of patients	Median survival (days)	95% CI
Good	0	26	390	320–493
Intermediate	1	37	279	189–349
Poor	2	3	80	35–129

Kaplan–Meier and Breslow test.
Abbreviations: CI, Confidence interval.

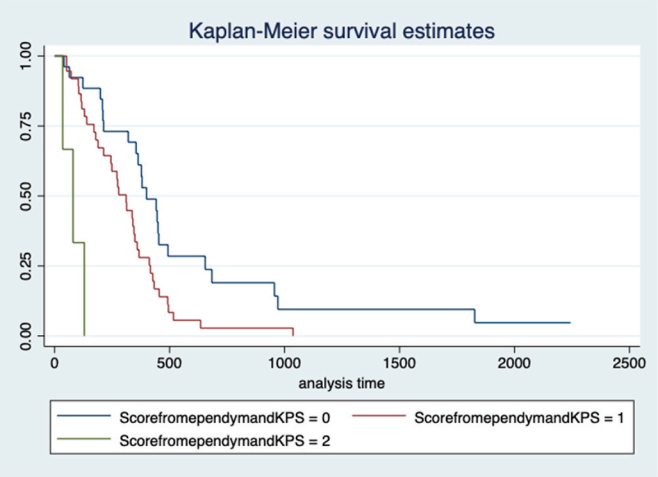

Fig. 2. Kaplan–Meier survival plots of patients in the study cohort *(n = 66)* stratified by the three prognostic groups according to NSGS defined by Park CK et al. Green line represent poor prognostic group (2 points), red line represent intermediate prognostic group (1 point), and blue line represent good prognostic group (0 points). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 4
Survival analysis to confirm the significant difference between the three prognostic groups defined by NSGS from Park CK et al.

Comparison of survival	Median survival (days)	HR	*p* value	95% CI
Good vs. Intermediate	390 vs. 279	2.06	0.009	1.19–3.55
Good vs. Poor	390 vs. 80	18.31	0.000	4.67–71.68
Intermediate vs. Poor	279 vs. 80	8.89	0.001	2.39–32.99

Kaplan–Meier and Breslow test.
Abbreviations: HR, Hazard Ratio. CI, Confidence interval.

was wide, Ki-67 should possibly be considered when deciding on repeat surgery. However, this should be further investigated in future studies.

Park JK et al found that KPS ≦ 80, tumor volume ≧ 50 cm^3, and tumor in eloquent areas defined by presumed motor and speech areas as well as close to M1 and M2 of the middle cerebral artery (MSM score) ≧ 2 were significantly associated with poor postoperative survival.[10] Carson et al found that factors associated with decreased overall survival included lower KPS, older age, and shorter time from initial diagnosis to recurrence.[8] Ammirati et al found that patients with KPS >70 before repeat surgery had longer survival.[7]

As expected, age was also a significant prognostic factor in the present study. Age is usually an important factor in e.g. adjuvant therapy,[15] and increasing age is usually associated with decreased survival.[18] Time between initial and repeat surgery was expected to have an effect on postoperative survival and was therefore included in the multivariable analysis, but no significant impact was found. However, in the present study, KPS was a more important factor.

The lack of guidelines for identifying and selecting patients who will benefit from repeat surgery has been addressed in previous studies, and various methods have been devised.[9,10] The results of the current survival analysis of the three NSGS prognostic groups were consistent with the results of Park CK et al.[9]

Based on the NSGS scoring system, patients were divided into three prognostic groups (range 0–2 points; 1 for KPS <70 and 0 for KPS ≧ 70; 1 for ependymal involvement and 0 for no ependymal involvement).[9] In our patients with a preoperative NSGS score that was good (0) or intermediate (1), surgical resection was associated with prolonged survival, and surgical resection may thus be indicated. We find that patients with a preoperative NSGS score of 2 (poor prognostic group) do not appear to have the same survival benefit of repeat surgery, which is consistent with the results of Park CK et al. Repeat surgery in the poor prognostic group should therefore only be performed after careful consideration. NSGS is a simple scoring method and is based on variables that are easily accessible, making it suitable for use in daily clinical practice.[9] It seems that NSGS can be used as a guide to determine which patients may benefit most from repeat surgery and might be improved by also considering Ki-67, tumor volume, age, and time between primary surgery and repeat surgery. However, improving NSGS was outside the scope of the current study.

Postoperative chemotherapy after repeat surgery in an intermediate prognostic group was previously associated with significantly longer postoperative survival.[9] In the present study, only four patients did not receive postoperative chemotherapy, so our data cannot confirm this (they scored 0, 1, 1 and 1 respectively according to NSGS). Previous studies have shown that postoperative treatment with e.g. bevacizumab, irinotecan, temozolomide, and lomustine, has a significant beneficial effect on survival in patients with recurrent glioblastoma.[1,15,19–21]

5. Limitations

The main limitation of the present study was the size of the cohort (66 patients, of whom only three had a score of 3 and thus belonged to the poor prognostic group). Patients who have poor performance scores and are in a clinically poor state are usually disqualified for surgery, and they were thus not included in the study, as we aimed to reproduce the study from Park CK et al. Despite the relatively small cohort, however, a difference between the good and intermediate prognostic groups could be confirmed.

Our multivariable analysis included 12 variables which is more than usual given our sample size (66 patients). Despite the small risk of over-analysing our data, we have allowed this after discussions with our statisticians in the interest of exploiting other possible important confounders.

Fourteen of the patients in the study had multiple repeat surgeries, but only the initial and second surgeries were included in the analysis to ensure that patients received the same preoperative treatment, and to have a more homogeneous patient population so that we could better compare the outcome from the individual patients. This can be a limitation, however, as the patients did not receive the same treatment after repeat surgery until their death (final outcome parameter).

Formula (A x B x C)/2 that was used to approximate the tumor volume assumes that the tumor is ellipsoid. Therefore, the more a tumor deviated from an ellipsoid shape, the less accurate the calculated volume would be. Although manual or automated volumetric measurements probably would have been more accurate, the (A x B x C)/2 formula is easy and is considered a good approximation.

The study is prone to selection bias due to its retrospective design, and a further limitation is the lack of a validation cohort e.g. from another hospital. This calls for multicenter and preferably prospective cohort studies.

6. Conclusions

In this study, several prognostic variables to predict postoperative survival in patients with recurrent glioblastoma were identified. These variables may be useful in daily clinical practice as an aid in predicting a patient's survival after repeat surgical treatment. The NSGS scoring system is an easy tool that could be used to help decide whether to proceed with surgical resection as we found significant differences in postoperative survival between the three NSGS prognostic groups. Patients in the good and intermediate prognostic groups appear to benefit from repeated surgery in terms of longer postoperative survival, and surgical resection may thus be indicated. Patients in the poor prognostic group do not appear to have the same survival benefit, and surgery should only be performed after careful consideration.

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Ethical approval

The study was performed in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

For this type of study formal consent is not required.

CRediT authorship contribution statement

Stella TE. Hansen: Writing – review & editing, Writing – original draft, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Kasper S. Jacobsen:** Writing – original draft, Supervision, Investigation, Data curation. **Mikkel S. Kofoed:** Software, Formal analysis. **Jeanette K. Petersen:** Writing – review & editing. **Henning B. Boldt:** Writing – review & editing. **Rikke H. Dahlrot:** Writing – review & editing. **Mette K. Schulz:** Writing – review & editing, Supervision, Project administration, Methodology. **Frantz R. Poulsen:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix 1. Univariate analysis results of prognostic factors

Variables	Median survival (days)		Univariate analysis, *p* value	HR *[95% CI]*
	Yes	No		
Male sex	131	345	0.525	1.18 [0.71–1.94]
Headache	334	337	0.863	1.05 [0.62–1.78]
MGMT methylated	354	249	0.094	0.63 [0.36–1.08]
Residual tumor at initial surgery	292.5	342.5	0.413	0.78 [0.43–1.41]
Residual tumor at second surgery	275	367	0.136	1.47 [8.89–2.45]
Right-side tumor location	372	276.5	0.107	0.66 [0.39–1.09]
Frontal	249	340	0.680	0.88 [0.49–1.58]
Temporal	337	334	0.375	1.32 [0.72–2.42]
Parietal	242	342.5	0.142	1.57 [0.86–2.88]
Occipital	462.5	312	0.222	0.63 [0.29–1.33]
Spanning several regions	331	335.5	0.560	0.81 [0.39–1.66]
EOR at recurrence >95%	349	311	0.489	0.84 [0.51–1.39]

Abbreviations: EOR, extent of resection. MGMT, O6-methylguanine-DNA methyltransferase. IDH1, Isocitrate dehydrogenase-1. HR, Hazard Ratio. CI, Confidence interval. N/A, not applicable.

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