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ARTICLE

Impact of surgical treatment on the performance status of patients with high-grade gliomas

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ABSTRACT

Objectives: The objective of our study is to evaluate the impact of neurosurgical operative treatment on the performance status assessed by the Karnofsky Performance Scale (KPS) in patients with HGG for the first, for the second intervention and for the different age groups.

Methods: A group of 425 patients operated consecutively for high-grade gliomas were included in this study. The performance status was evaluated preoperatively and 15 days postoperatively with the KPS. Analyses for the different histological grade, tumor locations and age groups divided by decades have been made.

Results: The initial, preoperative KPS score for patients with grade III tumor was 77.65 and for grade IV – 71.35. Following the first operation mean KPS has a statistically significant increase and reaches 82.24 and 78.41, respectively. The improvement of the performance status after the first operation was significant for all relevant age groups, including the sixth, seventh and eighth decades. Although the obtained mean KPS scores after the second operation did not show improvement there was also no clear evidence for worsening in this group of patients (n = 100) and the negative results obtained were not statistically significant.

Conclusion: According to our study, the first operation has a beneficial effect on the performance status in patients with HGG. The results for the second operation are more ambiguous, but there is no clear evidence for worsening of the KPS score after the second intervention. These results were relevant for all age groups, so we may expect amelioration in the performance status even in older patients.

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High-grade glioma; surgery; quality of life; Karnofsky Performance Scale; performance status

Introduction

High-grade gliomas (HGG) are the most frequent primary brain tumors with an annual incidence of 6 cases per 100,000 persons. They are characterized by rapid growth, early neurological impairment and inevitable progression. Despite all advancements in our knowledge about primary brain tumors, the prognosis remains dismal with an unavoidable recurrence and a 5-year survival of about 3%, which is one of the worst among any oncological diseases [1–4].

Surgery has proven to extend the survival in patients with HGG [5–8], being a crucial part of their multimodal treatment. However, because of the infiltrative nature of high-grade gliomas, the delicate balance between radicalism and avoidance of postoperative neurological deterioration remains a difficult task [9]. However, the influence of the surgical treatment on the performance status (PS) and consecutively on the health-related quality of life (HRQOL) in patients with HGG can be questionable [10–12].

The normal functioning, social and everyday activities of the patients might be severely affected by HGG even at the early stages of the disease [9]. Health-related quality of life indicator is considered an important criterion for the evaluation of the efficacy of treatment of oncological diseases including high-grade gliomas [13]. Among the most widely used tools for evaluation of the QOL in the neurosurgical practice are the generic questionnaire of the World Health Organization (WHOQOL-100), the generic SF-36 and the QLQ-C30 questionnaires. Karnofsky Performance Scale (KPS) [14] is an important component of the HRQOL assessment. KPS evaluates the physical functioning by a score from 0 (deceased) to 100 (lack of disease or symptoms). KPS has proven to be a reliable measuring tool [15] and actually is one of the most widely applied performance measurement scales [16,17].

The objective of our study is to evaluate the impact of neurosurgical treatment on the performance status assessed by Karnofsky Performance Scale score in patients with high-grade gliomas in patients for the first, for the second intervention and for the different age groups.

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Material and methods

Patients

For a period of 10 years, 425 patients were operated for high-grade gliomas at the Department of Neurosurgery of University Hospital 'Pirogov' and were included in this study. Ninety-eight patients (23.1%) were with grade III glioma and 327 (76.9%) – with grade IV.

Patient data including detailed neurological assessment, age, sex, localization of the tumor, type and number of interventions and evaluation of the performance status were collected either retrospectively (n = 215) or prospectively (n = 210).

In all cases, microsurgical technique for tumor resection has been used. During the 10-year period, a lot changed in our diagnostic and surgical armamentarium. We gradually introduced 1.5T and later – 3T MRI, MRI tractography and MRI spectroscopy, PET-CT. In the operating theater, we progressively adopted intraoperative ultrasound control, different techniques for intraoperative neurophysiological monitoring, protocol for awake craniotomies, 5-ALA fluorescence, neuronavigation. We started collecting samples for the established tumor bank and improved the immunohistochemical, genetic and epigenetic subtypisation of HGG.

Assessment of the performance status

The performance status of the patients was evaluated pre- and postoperatively with the Karnofsky Performance Scale. The postoperative assessment was performed on the 15th day after the intervention (±1 day). The mean values for pre- and postoperative scores for first and second interventions were analyzed for statistically significant differences. The data for the third operation were not analyzed in detail due to the very small sample size, rendering it statistically insignificant (Table 1).

Statistical analysis

The correlation between pre- and postoperative KPS score and other clinical parameters was examined. T-test was used to validate if the difference between the pre- and postoperative KPS scores was statistically significant. Patients were divided into Grade III and Grade IV HGG groups and the obtained mean scores were presented on Box Plot for the first intervention (Figures 1 and 2, respective to the histological groups). The estimated difference for each group was calculated. All of the calculated pre- and postoperative mean values for KPS score altogether with the estimated difference for each group after each operation are summarized in Table 1.

Results

The study included 425 patients: 191 women (45%) and 234 men (55%) with HGG. The mean age of the patients was 56.8 years (range 9.5–90.3). The mean age of men with grade III tumors was 47.8 years and for grade IV – 51.3 years. For women, the mean age was 57.5 years and 60.9 years, respectively.

KPS was assessed before and 15 (±1) days after the intervention in all patients. Reoperation was proposed to every patient with signs of recurrence, a relatively good condition (KPS >50) and an accessible lesion.

Only one operation was performed in 305 (71.8%) patients: 67 with grade III and 238 with grade IV tumors; two operations – in 100 (23.5%) patients: 21 with grade III and 79 with grade IV; three and more operations – in 20 (4.7%) patients: 10 with grade III and 10 with grade IV. For grade III tumors the extent of resection achieved during the first operation was: partial in 24 (24.5%) of the cases, subtotal – in 43 (43.9%) and gross-total – in 31 (31.6%) of the cases. For grade IV tumors respective figures were 41 (12.6%), 143 (43.7%) and 143 (43.7%).

The initial, preoperative KPS score for Grade III (KPS of 77.65) and Grade IV tumors (KPS of 71.35) was notably different and indicative of more severe functional impairment in glioblastoma multiforme.

Mean KPS amelioration for the first operation in Grade 3 tumors was 4.59 and for Grade 4 group – 7.06. The results were statistically significant.

For the second operation, the KPS deteriorate with 1.74 for Grade 3 and with 3.33 for the Grade 4 group, but we did not find these results to be significant (p = 0.7698 and p = 0.2754, respectively). Details about KPS pre- and postoperatively can be found in Table 1.

Table 1. Mean preoperative (PreOp) and postoperative (PostOp) KPS score for the first, second and third operation and grade III and grade IV tumors; difference (diff) and *t*-test.

	histology	*n*	% of all	KPS PreOp	KPS PostOp	diff	*p*
First operation	Grade III	67	15.8	77.65	82.24	4.59	**0.0075**
	Grade IV	238	56.0	71.35	78.41	7.06	**0.0000**
Second operations	Grade III	21	4.9	68.26	66.52	−1.74	0.7698
	Grade IV	79	18.6	71.31	67.98	−3.33	0.2754
Third operations	Grade III	10	2.4	53.33	51.11	−2.22	-
	Grade IV	10	2.4	56.25	47.50	−8.75	-

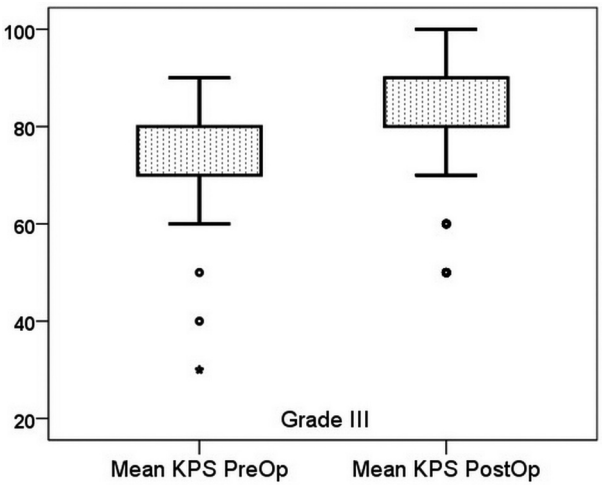

Figure 1. Boxplot comparing pre- and postoperative (first operation) KPS in Grade III glioma patients.

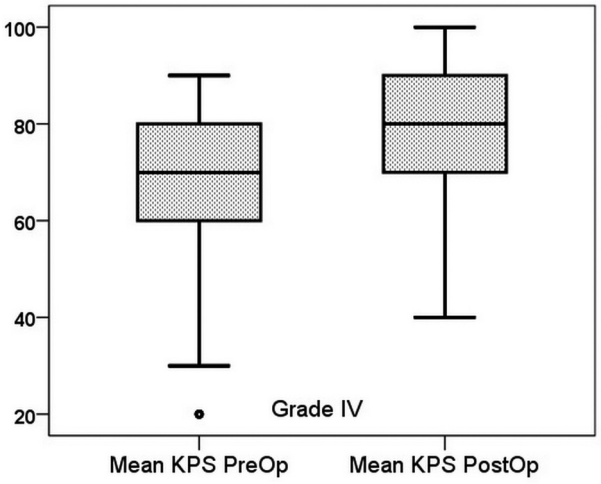

Figure 2. Boxplot comparing pre- and postoperative (first operation) KPS in Grade IV glioma patients.

For both left- and right-sided tumors a statistically significant improvement of KPS score was observed. In tumors with bilateral localization, the change in KPS was minimal and not statistically significant.

Patients operated in this series presented with a single lesion in 408 cases (96%). Multiple lesions occurred in 16 patients (4%) and in one patient a biopsy was performed due to diffuse HGG. Lesions on the right side were slightly more common than on the left side – 213 (50%) vs. 184 (43%), respectively, and in 28 cases (7%) lesions were bilateral.

Tumor localization was as follows: frontal lobe engagement in 144 cases (33.9%), parietal – 151 (35.5%), occipital – 53 (12.5%), temporal – 195 (49.9%), periventricular expansion – 23 (5.4%), more than one lobe – 139 (32.7%), cerebellar – 5 (1.2%), brainstem – 4 (0.9%). For all tumor localizations, the improvement of KPS was statistically significant except for periventricular and brainstem HGG.

Most of the patients were in their sixth and seventh decade (117 and 123 cases, respectively) and represented 56.47% of all patients. The distribution of the patients by age groups, pre- and postoperative KPS and t-test for the first operation can be found in (Table 2). The amelioration in the KPS score was statistically significant for patients in the third, fifth, sixth, seventh and eighth decade.

Table 2. Mean preoperative (PreOp) and postoperative (PostOp) KPS score for the different age groups per decade; difference (diff) and t-test.

Decade	*n*	% of all	KPS PreoOp	KPS PostOp	diff	p
1	1	0.2	30.00	60.00	30.00	-
2	3	0.7	76.67	80.00	3.33	-
3	20	4.7	72.00	83.00	11.00	0.0492
4	35	8.2	80.57	83.43	2.86	0.3174
5	56	13.2	75.71	82.50	6.79	0.0049
6	117	27.5	73.68	80.94	7.26	0.0001
7	123	28.9	71.87	77.48	5.61	0.0025
8	61	14.4	67.38	73.28	5.90	0.0297
9	8	1.9	66.25	81.25	15.00	-
10	1	0.2	80.00	80.00	-	-

Discussion

High-grade gliomas are the most common primary brain tumors representing significant health concern due to the poor prognosis, social impact and the economic appraisal.

Despite that some studies question the beneficial effect of surgery and the extent of the resection (biopsy versus complete excision) [18,19] a large amount of data has demonstrated that surgery improves the patient's outcome and survival [5–8,17,20–22] and actually surgical treatment presents a crucial part of the multimodal treatment. Lacroix et al. advocated that an extent of the surgical resection of ≥98% significantly improves the survival [6]. Sanai et al. put this burden to 78% [17] and other studies – to 90% [23].

Because of the infiltrative nature of high-grade gliomas, the delicate balance between the extent of tumor removal (radicalism) and avoidance of postoperative neurological deterioration remains a difficult task [9]. On one hand, 'too little surgery' would not lead to significant improvement of the symptoms and the prognosis, whereas aggressive surgery ('too much surgery') may be associated with greater risk of new neurological deficit and deterioration of HRQOL. In this perspective, the impact of surgery on the performance status and the HRQOL has become an increasingly important parameter in the complex evaluation of the performed therapy.

There is no universally accepted definition for the quality of life. It is defined by Ferrans as 'a person's sense of well-being that stems from satisfaction or dissatisfaction with the areas of life that are important to him/her' [24]. Different tools for measuring the QOL–questionnaires and surveys have been developed such as the SF-36, WHOQOL-100, QLQ-BN20 (EORTC). All these tools are considered appropriate, sensitive and reliable for the assessment of QOL in patients with

HGG and have been adapted to various languages [25,26]. Using these scales can play a significant role in determining individual needs and preferences of patients, comparing the effectiveness of treatment and monitoring the quality of provided care.

KPS is one of the best known and most widely applied scales in neurosurgery [16,17] and it has proven to have a prognostic value for the survival of patients with HGG [27,28]. KPS generally correlates well with the overall QOL, but KPS is relevant only to the measurement of the functional ability [19,29]. Despite that, it was applied as a QOL measurement tool in several studies [30,31].

Budrukkar et al. determined the KPS score as a significant factor that defines the global QOL. The authors conclude that patients with a performance status lower than 70 had a lower global QOL compared to patients with KPS score more or equal to 80 including all histological types of high-grade gliomas [18]. The KPS gives an additional benefit, as it is an external measure that may be useful in studies on HRQOL among patients who are unable to provide reliable self-reported information. Some criticism has been mentioned regarding the lack of sensitivity of KPS in patients with a high score (KPS 80–100) – KPS was not able to predict depression, neither was reliable in assessing well-being, socializing and patients' performance status [29,32]. Despite all KPS remains one of the most widely used scales for measurement of the QOL with proven prognostic value for the extent of survival in patients with HGG.

According to our study, the resection of high-grade gliomas may provide a prompt improvement of the patient's performance status. Fifteen days after the first operation, we documented a statistically significant increase of the mean KPS score, with 4.59 points up to 82.24 for the patients with Grade III tumors and increase with 7.06 points up to 78.41 for the patients with Grade IV gliomas (Table 1). The documented amelioration of the KPS score was valid for tumors with left- and right-side localization but not for lesions with bilateral extension. The amelioration was valid also for tumors involving the frontal, the parietal, the occipital or temporal lobe, for tumors involving more than one lobe and for tumors with cerebellar localization but not for periventricular and brain stem tumors.

The reoperation of recurrent HGG is a contradictory topic. Some authors suggest that a second even third operation can be beneficial for the extent of survival [33–35]. This opinion is not accepted unanimously regarding the rising number of complications, the questionable advantage for the survival and the potential decrease in HRQOL [36–38].

In our study, a second operation was performed in 100 patients (23.5%). For both groups, a slight decline in KPS was observed (Table 1) but these results were not statistically significant. We have also to take into consideration that the recovery after a reoperation is usually longer so the 15-day period for the postoperative KPS assessments was probably too short. Consequently, our study suggests that the second intervention does not influence negatively the performance status of the patients.

Age has been frequently discussed as an important prognostic factor in patients with HGG [16,39–46]. In a study by Casartelli et al. from 2009, a cohort of 196 patients with HGG was investigated for different prognostic factors for survival. They observed that patients diagnosed at an older age (>64 years) had a significantly higher hazard as compared to younger patients (≤64 years), to survive shorter [39]. Giuseppe Minniti et al. put this burden at the age of 70 [40]. Regarding the higher risk related to surgery, the co-morbidities and the slower mobilization, age is considered as an important prognostic factor in all large studies [16,41–46].

Most of the patients of our study (56.47%) were in their sixth and seventh decade (Table 2). With the advancement of the age at diagnosis, we observed a decline in the preoperative KPS score: from 80.57 for patients in their fifth decade to 66.25 for patients in their ninth decade. Amelioration in the KPS score after the first operation was statistically significant for patients in their third, fifth, sixth, seventh and eighth decade. Based on these results we can conclude that the first operation has a beneficial effect on the performance status of patients for all age groups hence we can expect a higher postoperative KPS score even in older patients.

Regarding the infiltrative nature of HGG our striving for total or even supratotal excision is in delicate balance with the potential risk of postoperative neurological deficit. The introduction of diagnostic tools as MRI tractography, MRI spectroscopy, functional MRI [47] and surgical techniques as intraoperative ultrasound control, different techniques for intraoperative neurophysiological monitoring [48,49], protocol for awake craniotomies, 5-ALA fluorescence, neuronavigation and intraoperative MRI have vastly ameliorated our possibilities to achieve more radical surgical excision with less risk to deteriorate the neurological state and performance status of the patient. Despite all that, we are still far from the complete control over the potential postoperative neurological deficit [50]. Accessing the influence of the different diagnostic and surgical techniques over the performance status in our series is a difficult task that is beyond the scope of this study. Our overall data suggest that for the 10-year period, the difference between the preoperative and postoperative KPS score remains relatively constant – around 6.5. These mean that our technological advancement has influenced our possibility to detect and resect HGG but the influence over the performance status is questionable and further investigation in this field is required.

Conclusion

According to our study, the first operation has a beneficial effect on the performance status of patients with high-grade gliomas. The results for the second operation are more ambiguous, but there is no clear evidence for worsening after the second intervention. This observation was relevant for all age groups, so we may expect amelioration in the performance status even in older patients.

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Disclosure statement

NG, ML, GP, NV, MK, RK, StG have nothing to disclose.

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