Association of perioperative adverse events with subsequent therapy and overall survival in patients with WHO grade III and IV gliomas

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Abstract

Purpose

Maximum-safe-resection followed by chemoradiotherapy as current standard of care for WHO grade III and IV gliomas can be influenced by the occurrence of perioperative adverse events (AE). The aim of this study was to determine the association of AE with the timing and choice of subsequent treatments as well as with overall survival (OS).

Methods

Prospectively collected data of 283 adult patients undergoing surgery for WHO grade III or IV gliomas at the University Hospital Zurich were analysed. We assessed basic patient characteristics, Karnofsky performance score (KPS), extent of resection (EOR), WHO grade, and we classified AE as well as modality, timing of subsequent treatment (delay, interruption or non-initiation) and OS.

Results

In 117 patients (41%), an AE was documented between surgery and 3-months follow-up. There was a significant association of AE with an increased time to initiation of subsequent therapy ($p = 0.005$) and a higher rate of interruption ($p < 0.001$) or non-initiation ($p < 0.001$). AE grades correlated with time to initiation of subsequent therapy ($p = 0.038$). AE were associated with shorter OS in univariate analysis ($p < 0.001$).

Conclusion

AE are associated with delayed and/or altered subsequent therapy and worse OS in WHO grade III and IV glioma patients. These data emphasize and quantify the importance of safety within the maximum-safe-resection concept.

Introduction

The current standard treatment for WHO grade III and IV gliomas is maximum-safe resection followed by radiotherapy plus/minus concomitant and maintenance alkylating-agent based chemotherapy [1]. Adverse events (AE) are an important and sensitive parameter in measuring management quality of the perioperative period [2]. Importantly, AE occur frequently during and after neurosurgical interventions and are associated with poor functional status [3-5].

AE are considered to affect the course of further therapy and might lead to non-initiation, interruption or delay of subsequent therapy and eventually to worse overall survival (OS) [5, 6]. However, the association

of treatment delay of therapy and OS remains controversial. Although the relevance of the exact timing of subsequent therapy remains uncertain, a systemic review [7] and different studies [8-14] seem to agree that a moderate delay of subsequent chemoradiotherapy does not have a detrimental effect on OS, but a delay of more than 42 days after surgery might be associated with worse OS.

Here, we analyzed the association between perioperative AE and both, the timing of subsequent therapy as well as OS.

Methods

Study design and patient selection

We prospectively collected data from the patient registry of the Department of Neurosurgery at the University Hospital Zurich [4]. We screened all patients with surgery for anaplastic astrocytoma (WHO grade III) or glioblastoma (WHO grade IV) for eligibility between January 2013 and June 2017. All adult patients with a complete dataset regarding the timing and modality of subsequent therapy and the occurrence of AE were included. Deaths before June 2019 were ascertained and patients were censored at the last date they were stated to be alive.

Treatment

All included patients underwent initial neurosurgical intervention for WHO grade III or IV glioma. Extent of resection (EOR) varied between biopsy-only, partial resection <98% and gross total resection $\geq 98\%$. The protocol of subsequent therapy during the study period was based on the current EANO guideline [15]. The standard fractionated radiotherapy usually consisted of a dose 60 Gray. First line chemotherapy for glioblastoma during the study period was concomitant temozolomide during radiotherapy followed by 6 cycles of maintenance temozolomide. In case of progression or relapse under the first line treatment with temozolomide, second line chemotherapeutics (mostly CCNU) or bevacizumab were used.

Study variables

Parameters extracted from the patient registry were age, sex, functional state, EOR, WHO grade, procedure and timing of subsequent therapy, any delay or interruption or non-initiation of the subsequent therapy protocol, the occurrence of AE, and OS. The patients' functional state was quantified using the Karnofsky performance score (KPS). A worsened functional state was defined as a decrease of the KPS by 10% or more 3 months postoperatively compared to the preoperative KPS. EOR was assessed by three-dimensional volume measurements of pre- and <72 h postoperative MRI using Smartbrush application of Brainlab Elements, Brainlab AG Munich. In case of lacking MRI data, EOR was not further evaluated.

Perioperative AE with its corresponding clinical diagnosis were assessed using the Clavien-Dindo-Grade (CDG) classification and graded accordingly (see Online Resource 1) [16].

We defined the variable *altered subsequent therapy* as the occurrence of either a delay, interruption or non-initiation of subsequent therapy. The time to initiation of subsequent therapy was defined as duration between the intervention and the beginning of subsequent therapy. A delay in subsequent therapy was defined as a duration of more than 42 days until initiation. Any interruptions of therapy were additionally registered and defined as any break in the protocol of subsequent therapy. The non-initiation of subsequent therapy was defined as the absence of subsequent chemo- and radiotherapy.

OS was defined as the time from surgery until death or the last date when the patient was known to be alive.

Statistical methods

The patient registry is based on FileMaker Pro version 13.0. For statistical analysis and creation of graphs IBM SPSSv24 and MATLAB R2019a were used. A p-value of ≤ 0.05 was considered significant. Continuous data was analyzed with two-tailed Mann-Whitney U-tests and Student's *t*-tests and categorical data with two-sided Pearson χ^2 -tests, correlations using Spearman correlation tests, OS using Kaplan-Meier and Log Rank tests and multivariate analysis using Cox's proportional hazard model. Hazard ratios (HR) are given with 95% confidence intervals (CI).

Results

Patient characteristics and outcome data

Of the 283 included patients, the main clinical characteristics and outcome data stratified for AE are depicted in Table 1. A statistically significant difference in patient characteristics between patients with AE and patients without AE was seen for age, preoperative KPS, at discharge and at 3 months postoperatively as well as therapy groups. For the outcome data, a statistically significant difference between the subgroups was found for worsened functional state 3 month postoperative, altered subsequent therapy, delay in subsequent therapy, interruption, non-initiation and median OS.

Table 1 Patient characteristics and outcome variables stratified for AE. AE, adverse event. EOR, extent of resection.. KPS, Karnofsky performance score. IQR, interquartile range. SD, standard deviation. CI, confidence interval. ^a at least one AE from surgery to 3 months postoperatively. ^b KPS 3 months postoperatively compared to peroperative KPS. ^c at least one AE prior to start of subsequent therapy. ^d Mann-Whitney U-test. ^e χ^2 -test. ^f Student's *t*-test. ^g Log Rank test. * statistically significant

Patient characteristics and outcome variables stratified for AE				
Variables	Overall (n = 283)	no AE (n=166)	AE (n=117) ^a	p-Value
Median age, years (IQR)	63 (52-72)	61 (52-69)	67 (54-74.5)	0.005^{d*}
Female, n (%)	95 (34)	58 (35)	37 (32)	0.561 ^e
Glioblastoma WHO grade IV, n (%)	245 (87)	139 (84)	106 (91)	0.095 ^e
Extent of resection, n (%)				
Biopsy only	89 (31)	47 (28)	42 (36)	0.176 ^e
Partial resection (EOR < 98%)	114 (40)	72 (43)	42 (36)	0.207 ^e
Gross total resection (EOR ≥ 98%)	69 (24)	42 (25)	27 (23)	0.668 ^e
Unclear extent of resection	11 (4)	5 (3)	6 (5)	0.364 ^e
Therapy groups, n (%)				
Chemoradiotherapy	174 (62)	116 (70)	58 (50)	<0.001^{e*}
Chemotherapy	33 (12)	22 (13)	11 (9)	0.320 ^e
Radiotherapy	45 (16)	22 (13)	23 (20)	0.147 ^e
No other therapy than best supportive care	31 (11)	6 (4)	25 (21)	<0.001^{e*}
Median KPS score preoperatively, % (IQR)	80 (70-90)	80 (70-90)	80 (70-90)	0.009^{d*}
Median KPS score at discharge, % (IQR)	80 (70-90)	90 (80-90)	70 (50-80)	<0.001^{d*}
Median KPS score at 3 months postoperatively, % (IQR)	80 (60-90)	90 (80-90)	60 (15-80)	<0.001^{d*}
Worsened functional state ^b , n (%)	130 (46)	56 (33)	74 (63)	<0.001^{e*}
Mean time to initiation of subsequent therapy, days (SD)	32 (12)	30 (8.5)	35 (17) ^c	0.005^{f*}
Altered subsequent therapy, n (%)	82 (29)	23 (13)	59 (50)	<0.001^{e*}
Delay (>42d) in subsequent therapy	28 (11)	12	16	0.016^{e*}

		(7.5)	(17) ^c	
Interruption	29 (10)	5 (3.0)	24 (21)	<0.001 ^{e*}
Non-initiation	31 (11)	6 (3.6)	25 (21)	<0.001 ^{e*}
Median overall survival, months (95% CI)	13 (11.3-14.7)	17 (14.5-19.5)	9 (6.7-11.3)	<0.001 ^{g*}

AE are associated with delay and altered subsequent treatment

The mean time to initiation of subsequent therapy was significantly higher for patients with AE prior to therapy ($p = 0.005$) and correlated significantly with the grade of AE ($p=0.038$, Spearman's $\rho = 0.13$, Fig. 1a). Altered subsequent therapy in general and each of the underlying variables (either *delay* or *interruption* or *non-initiation* of the subsequent therapy) was more frequent in the subgroup of patients with AE (Table 1).

Additionally, there was a significant correlation between the severity of CDG and KPS at discharge from hospital ($p < 0.001$, Spearman's $\rho = -0.41$) with a slope of -9.5 KPS points per increment of Clavien-Dindo-Grade in the linear fit (see Fig. 2).

AE are associated with worse OS

OS for patients with AE was shorter ($p < 0.001$) (Table 1, Fig. 1b). However, there was no significant correlation between the CDG of the AE and OS ($p = 0.063$). Altered subsequent therapy and its underlying variables *interruption* and *non-initiation* were also associated with a significant decrease in OS (Fig. 1c, 1d). However, the delay itself was not associated with a change in OS ($p = 0.113$, Fig. 1d).

A multivariate Cox proportional hazard model was conducted to estimate the association of occurrence of AE and altered subsequent therapy with OS (adjusted for confounders age, sex, WHO grade, preoperative KPS and EOR). There was a trend towards shorter OS in patients with AE with HR = 1.32 (CI 0.96-1.77), although this did not reach statistical significance ($p = 0.063$). Altered subsequent therapy had a stronger and significant association with shorter OS (HR = 1.97, CI 1.44-2.69, $p < 0.001$) (see Table 2).

Table 2 Predictor of overall survival (OS). The putative predicting factors for OS as AE and altered subsequent therapy were analyzed using a Cox proportional hazard model correcting for confounders. AE, adverse event. KPS, Karnofsky performance score. SE, standard error. * statistically significant

Prognostic factors of overall survival				
Variables	Coefficient Exp(B)	SE	95% CI	p-Value
Occurrence of AE from surgery to 3 months postoperatively	1.32	0.15	0.99 - 1.77	0.063
Altered subsequent therapy	1.97	0.16	1.44 - 2.69	<0.001*
Age	1.04	0.01	1.03 - 1.05	<0.001*
Male sex	0.99	0.14	0.75 - 1.31	0.949
Tumor grade (WHO grade)	2.28	0.27	1.33 - 3.89	0.003*
Preoperative KPS	0.99	<0.01	0.98 - 0.99	0.003*
Extent of resection (reference category <i>biopsy only</i>)				
Partial resection	0.65	0.16	0.47 - 0.90	0.008*
Gross total resection	0.50	0.19	0.35 - 0.72	<0.001*
Unclear extent of resection	0.79	0.36	0.39 - 1.59	0.514

Discussion

There is only scarce information on the frequency and the exact clinical repercussions of AE in glioma surgery. The risk of AE in the resection of WHO grade III and IV glioma is relatively high due to the difficult balancing between a goal of maximal tumor resection and new postoperative neurological deficits and other AE [5]. Therefore, knowing the consequence of a perioperative AE is of utmost importance.

The impact of timing of subsequent therapy on OS is still unclear. Nevertheless different studies indicate that a delay of more than 42 days should be avoided [7-12]. We observed a significantly higher mean time to initiation of subsequent therapy and a corresponding higher rate of delay of more than 42 days for patients with an AE. We also observed that AE with higher CDG scores were associated with a longer time to initiation. These findings emphasize that surgical AE can entail a suboptimal timing and course of subsequent therapy. In addition, our findings indicate that patients with AE are less likely to receive standard of care therapy; the rate of delay, interruption and non-initiation is significantly higher.

Regarding OS, patients with AE had significantly decreased median survival on univariate analysis in line with previous studies [5, 17]. On multivariate analysis, patients with AE had a strongly increased hazard ratio adjusted for possible confounders, although the result was not significant, likely due to the relatively small size of the study group. The potential detrimental effect of AE on OS can be explained by the direct negative effect of AE on the patient's health status, and furthermore by a higher rate of altered subsequent therapy. The association of non-initiation and interruption of subsequent therapy with decreased OS was clearly shown in this study. However, we did not find any evidence showing that a delay of more than 42 days of subsequent therapy alone is associated with inferior OS.

As a retrospective analysis of prospectively collected data, our study is subjected to the general limitations of retrospective studies. Still, our outcome data was collected prospectively and modified retrospectively only in case of incompleteness, which mimized the risk of information bias.

In conclusion, our results support the hypothesis that AE reduce the rate of successful and uninterrupted chemoradiotherapy and ultimately limit OS. In the sensitive balancing act between maximal resection and postoperative neurological function, our study quantifies the risk of causing AE and by that a possible impairment of the course of subsequent therapy and OS. Therefore, these findings have implications in risk stratification and quality management of WHO grade III and IV glioma surgery.

Declarations

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Conflicts of interest/Competing interests: No conflict of interest or competing interests stated by any author.

Ethics approval: The local ethics committee (Kantonale Ethikkommission Zürich) approved prospective data collection in the patient registry and waived patient consent due to the observational nature of the study (PB-2017-00093). The prospective data collection was registered at clinicaltrials.gov (NCT01628406). The study followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) recommendation for observational studies.

Consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and material: The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Code availability: Not applicable .

Authors' contributions: Study design: L.W., J.S., M.C.N. Data acquisition: L.W., T.M., J.V., F.V., S.V., L.P., J.S., M.C.N. Statistical analysis: L.W. Interpretation: all authors. Writing of original draft: L.W. Review and

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Figures

Figure 1

CDG grade, KPS and subsequent therapy. a: Of all 252 cases with any subsequent therapy, in 75 cases an AE prior to beginning of subsequent therapy was noted. The time to initiation and the CDG grade were correlated with Spearman's $\rho=0.13$ ($p = 0.038$). The linear fit has a slope of 3.9 days per increment of CDG. b: The occurrence of AE until 3 months postoperatively is associated with a significantly lower OS in Log Rank test ($p < 0.001$). c: The occurrence of altered subsequent therapy is associated with a significantly lower OS in Log Rank test ($p < 0.001$). d: The subgroups with interruption or non-initiation of subsequent therapy had both a significant decreased OS ($p < 0.001$). The subgroup with delay showed no significant association with OS ($p = 0.113$).

Figure 2

CDG grade and KPS. Over all 283 patients, in 78 patients at least one AE occurred before discharge. KPS and CDG at discharge were correlated with Spearman's $\rho = -0.41$ ($p < 0.001$). The linear fit had a slope of -9.5 KPS points per increment of CDG

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