Journal of Neuro-Oncology
https://doi.org/10.1007/s11060-020-03393-z

CLINICAL STUDY

Resection of recurrent glioblastoma multiforme in elderly patients: a pseudo-randomized analysis revealed clinical benefit

Mateo Tomas Fariña Nuñez[1,2,7] · Pamela Franco[1,2,7] · Debora Cipriani[1,2,7] · Nicolas Neidert[1,2,7] · Simon P. Behringer[1,2,7] · Irina Mader[3,4] · Daniel Delev[5] · Christian Fung[2,7] · Jürgen Beck[2,7] · Roman Sankowski[6,7] · Nils Henrik Nicolay[7,8] · Dieter Henrik Heiland[1,2,7] · Oliver Schnell[1,2,7]

Received: 30 October 2019 / Accepted: 7 January 2020

Abstract

Introduction Elderly patients constitute an expanding part of our society. Due to a continuously increasing life expectancy, an optimal quality of life is expected even into advanced age. Glioblastoma (GBM) is more common in older patients, but they are still often withheld from efficient treatment due to worry of worse tolerance and have a significantly worse prognosis compared to younger patients. Our retrospective observational study aimed to investigate the therapeutic benefit from a second resection in recurrent glioblastoma of elderly patients.

Materials and methods We included a cohort of 39 elderly patients (> 65 years) with a second resection as treatment option in the case of a tumor recurrence. A causal inference model was built by multiple non- and semiparametric models, which was used to identify matched patients from our elderly GBM database which comprises 538 patients. The matched cohorts were analyzed by a Cox-regression model adjusted by time-dependent covariates.

Results The Cox-regression analysis showed a significant survival benefit (Hazard Ratio: 0.6, 95% CI 0.36–0.9, p-value = 0.0427) for the re-resected group (18.0 months, 95% CI 13.97–23.2 months) compared to the group without re-resection (10.1 months, 95% CI 8.09–20.9 months). No differences in the co-morbidities or hemato-oncological side effects during chemotherapy could be detected. Anesthetic- and surgical complications were rare and comparable to the complication rate of patients undergoing the first-line resection.

Conclusion Taken together, in elderly patients, re-resection is an acceptable treatment option in the recurrent state of a glioblastoma. The individual evaluation of the patients′ medical status as well as the chances of withstanding general anesthesia needs to be done in close interdisciplinary consultation. If these requirements are met, elderly patients benefit from a re-resection.

Keywords Recurrent glioblastoma multiforme · Elderly patients · Re-Resection

Introduction

Glioblastoma multiforme (GBM) is the most common and most aggressive primary malignant brain tumor in adults [1]. With a median overall survival (OS) of about 20 months [2], it is associated with a particularly poor prognosis especially in elderly patients [1]. This group has not only the highest GBM incidence but also the worst median OS of approximately 6 months [3–5]. The current standard treatment of GBM, first published by Stupp et al., involves maximal extent of surgical resection (EOR) followed by 6 weeks of radiotherapy (RT) with concomitant and adjuvant temozolomide (TMZ) chemotherapy (RCT) [6]. However, elderly patients over 70 years were initially excluded from the study [7]. Further investigations demonstrated that overall prognosis for elderly patients treated alone with standard radiotherapy is poor, whereas TMZ chemotherapy or a combined therapy would present a potential alternative [8], especially in consideration of the MGMT promoter-methylation-status as a strong predictor of benefit [8, 9]. Hence, these data and the underrepresentation of elderly patients in clinical trials due to significant comorbidities [5] make the initial treatment of GBM in this population a challenge.

✉ Mateo Tomas Fariña Nuñez
mateo.farina@uniklinik-freiburg.de

Extended author information available on the last page of the article

Complete resection of at least all contrast enhancing tumor in GBM is correlated with a better outcome not only in the younger population [10, 11], but also in elderly cohorts [12, 13]. However, even if maximal safe resection -with the goal of complete resection is achieved, recurrence in GBM is inevitable [11]. There is only a little evidence regarding the best course of treatment when facing a GBM recurrence [14, 15]. In older patients in particular, it remains unclear to what extent additional treatment, including surgical interventions, would be appropriate. This study attempts to retrospectively evaluate this issue by developing a matched-cohort time dependent analysis to present data regarding the effect of re-resection for a homogeneous elderly patient population with recurrent primary GBM, after initial treatment including complete as well as partial resection and fractionated RT and/or TMZ chemotherapy (Table 1).

Materials and methods

Patient cohort: elderly patients Freiburg

The analyses are based on an institutional and previously published database of elderly patients (> 65 years) suffering from glioblastoma multiforme WHO°IV IDH wild-type. The database contained 538 patients. All patients received a neurosurgical intervention at the Department of Neurosurgery, University Hospital Freiburg, Germany between 2008 and 2018. An informed consent for the scientific exploration of clinical and biological data consistent with the local ethical standards and the Declaration of Helsinki was available from all patients. The study was approved by the local ethic committee and registered in the regional WHO database of clinical studies. The methods were carried out in accordance with the approved guidelines. Written informed consent was obtained from all patients. Postoperative 48 h/72 h-MRI was performed in order to evaluate the extent of resection, defined as gross-total resection with less than 5% residual tumor and partial resection with > 5% residual contrast enhancement in the T1-weighted MRI sequences.

Model of matched-cohorts

39 elderly patients received a resection of their recurrent tumor. The primary endpoint of the study was to investigate the effect of re-resection in elderly patients. In order to reduce statistical bias, we computed parametric models for causal inference to identify well-adjusted subsets of the re-resected (n = 39) and control cohort (Elderly database n = 538). The computational model implemented the algorithm published by Ho, Imai, King and Stuart (2004) to optimize parametric models by preprocessing data by non-parametric methods. The R-software implemented package *"MatchIt"* implements a wide range of models and was used to compute a model based on previously identified outcome dependent parameters. We validated the matched-cohort by t-Distributed Stochastic Neighbor Embedding (t-SNE) and propensity score.

Cox-regression model

We used the Kaplan–Meier method implemented in the "survival" package in R-software, to estimate overall survival and log-rank tests for comparisons of our matched-cohort. Median survival with 95% confidence intervals was shown. Hazard ratios and 95% confidence intervals were estimated by a Cox proportional-hazards regression model including a tenfold cross-validation. The alpha-level was determined to 5% to achieve statistical significance with a power of > 80%. Patients who continue to live or whose survival is not evident are censored in the analysis.

Cox-regression model with time-dependent covariates

The meaningfulness of a classical Cox proportional-hazards regression model is strongly biased due to the fact that only patients with improved survival may receive an additional surgery at a later stage. This bias is only partially reduced by the matched-cohort model. To address this issue, a Cox proportional-hazards regression model with re-resection as a time-depended-covariates was computed. The variable 're-resection' was split into its individual time intervals and analyzed by an adapted Cox proportional-hazards regression model. Additional, multivariate regression was performed including outcome-dependent variables.

Statistical data handling

Descriptive statistics were used to give an overview of the patient collective. Student's T-Test, Chi^2 and single as well as multifactorial ANOVA where used to compare our collective. Normal distribution was analyzed using Kolmogorov–Smirnov and Shapiro-Wilks-Test. For normal distributed parameters, mean and 95% confidence interval was reported. For non-normal distributed parameters median and interquantile range (IQR) was calculated.

Results

In this retrospective study, we enrolled 538 elderly patients with documented GBM. Therefrom, we identified a total of 39 Patients who underwent surgery at recurrence in the context of a tumor relapse. In order to reduce the bias, which arises from the diverse architecture of clinical parameters in

Table 1 Demographic data of the patient collective

	Single resection (n = 39)	Re-resection (n = 39)	Significance
Adjuvant therapy			
Chemotherapy (CT)	3 (7.7%)	7 (17.9%)	n.s
Radiotherapy (RT)	9 (23.1%)	8 (20.5%)	n.s
Radiochemotherapy (STUPP)	27 (69.2%)	24 (61.5%)	n.s
Age	69.8 IQR(6)	70 IQR(5.7)	n.s
Extent of resection			
First surgery			
GTR	36 (92.3%)	31 (79.5%)	n.s
Partial	3 (7.7%)	8 (20.5%)	n.s
Second resection			
GTR	–	36 (92.3%)	–
Partial	–	3 (7.7%)	–
Localization			
Frontal	13 (33.3%)	14 (35.9%)	n.s
Parietal	8 (20.5%)	7 (17.9%)	n.s
Temporal	4 (10.3%)	5 (12.8%)	n.s
Occipital	14 (35.9%)	13 (33.3%)	n.s
Sex			
Female	12 (30.8%)	13 (33.3%)	n.s
Male	27 (69.2%)	26 (66.7%)	n.s
KPS			
Preoperative	100% IQR(0)	100% IQR (0)	n.s
Postoperative	100% IQR(0)	100% IQR (0)	n.s
Tumor recurrence			
Local recurrence	38 (97.4%)	38 (97.4%)	n.s
Distant recurrence	1 (2.6%)	1 (2.6%)	n.s
Hospitalization (days)	7 IQR(3.5)	9 IQR(2)	n.s
Molecular marker			
MGMT methylated	20 (51.3%)	18 (46.2%)	n.s
MGMT unmethylated	9 (23.1%)	13 (33.3%)	n.s
MGMT unknown	10 (25.6%)	8 (20.5%)	n.s
IDH1/2 mutation	0 (0%)	0 (0%)	n.s
IDH1/2 wild-type	36 (92.3%)	38 (97.4%)	n.s
IDH1/2 unknown	3 (7.7%)	1 (2.6%)	n.s
Adverse events surgery	2 (5.1%)	2 (5.1%)	n.s
Motoric deficits	1 (2.6%)	1 (2.6%)	n.s
Aphasia	0 (0%)	1 (2.6%)	n.s
Anopsia	2 (5.1%)	1 (2.6%)	n.s
Infection	1 (2.6%)	0 (0%)	n.s
Medical AE	0 (0%)	0 (0%)	n.s
ASA score	2 IQR(0)	2 IQR(0)	n.s
Diabetes melitus	2 (5.1%)	3 (7.7%)	n.s
Hypertonia	16 (41%)	18 (46.2%)	n.s
Coronary disease	6 (15.4%)	8 (20.5%)	n.s
Anticoagulation	8 (20.5%)	8 (20.5%)	n.s

IQR interquartile range, *Partial* partial resection, *GTR* gross-total resection, *n.s.* no significance

retrospective analyses, a causal inference model was built by multiple non- and semiparametric models which were used to identify 39 matched patients from our Freiburg elderly GBM database (Fig. 1a). Furthermore, we then validated the distribution of our matched-cohort by t-Distributed Stochastic Neighbor Embedding (t-SNE) (Fig. 1b) and propensity

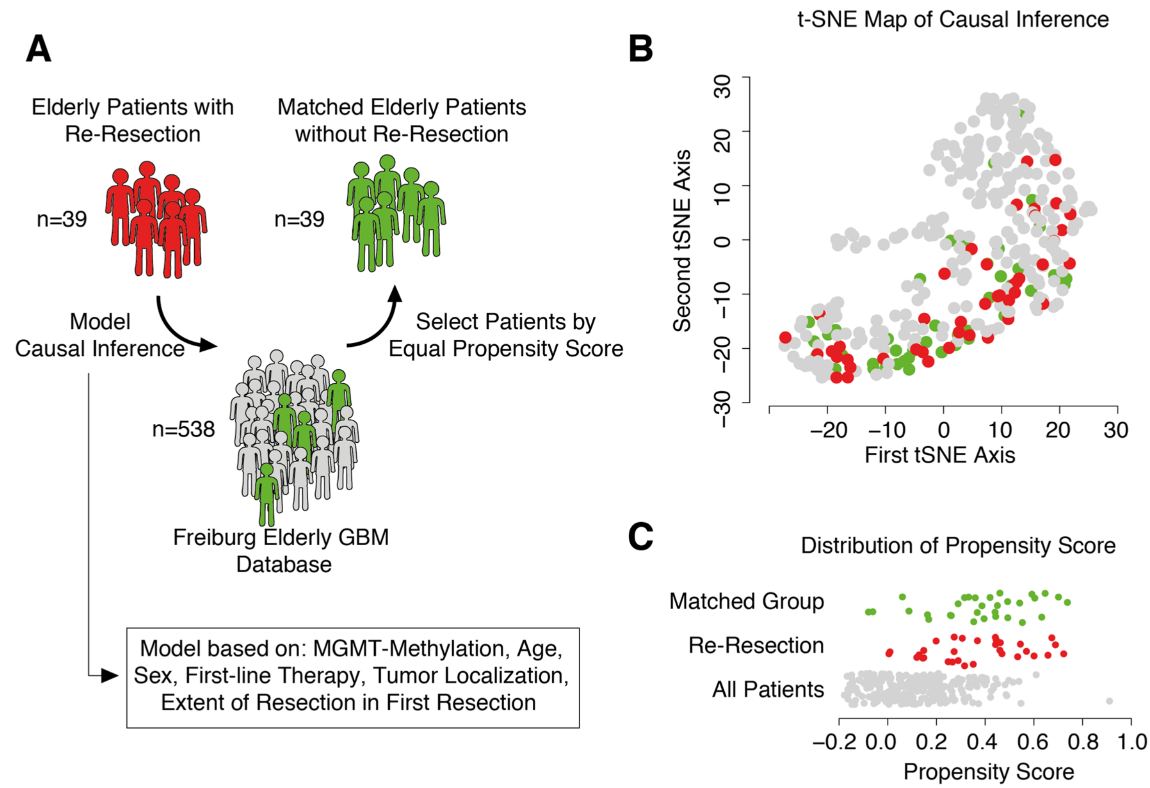

Fig. 1 Computational model to match cohorts. **a** 39 Patients who underwent a re-resection (green) were matched with 39 patients who did not have surgery at GBM recurrence (red). The selection was based on a model of causal inference based in multiple co-variables and ultimately in similar propensity scores. **b** T-distibuted stochastic neighbor embedding for visualization of the distribution of the matched cohorts. **c** Distribution of the propensity score for patients undergoing a re-resection (green), single resection (red) in comparison with all patients in the Freiburg eldery GBM database

score (Fig. 1c). As a result, we were able to significantly improve the distribution of outcome relevant clinical parameters within our comparative cohorts through our model.

Clinical characteristics

In our cohort of 78 elderly patients (39 surgery at GBM recurrence, 39 matched elderly patients), the median age of the 39 patients who underwent a re-resection was 70 (IQR 5.7); 13 patients (33.3%) were female and 26 (66.7%) male with a preoperative and postoperative KPS of 100 (IQR 0). 31 Patients (79.5%) received a gross total resection during the first surgery whereas 36 (92.3%) experienced similar resections during the re-resection. GBM localization was primarily frontal (35.9%), followed by occipital (33.3%), parietal (17.9%) and temporal (12.8%). MGMT Promoter-methylation-status was unmethylated in 13 patients (33.3%), methylated in 18 (46.2%), unknown in 8 (20.5%). Confirmed IDH1/2-mutation was not present in this cohort (0%). In 38 patients (97.4%) the IDH1/2-status was wild-type, in 1 patient (2.6%) the mutation-status remained unknown. After resection, 24 patients (61.5%), 8 (20.5%) and 7 (17.9%) underwent combined RT and TMZ [2], RT and TMZ alone, respectively.

The median age of elderly patients who underwent a single resection was 69.8 years (IQR 6) with a preoperative and postoperative Karnofsky performance status (KPS) of 100% (IQR 0). There were 12 females (30.8%) and 27 males (69.2%). Regarding GBM localization, 13 patients (33.3%), 8 (20.5%), 4 (10.3%) and 14 (35.9%) presented with frontal, parietal, temporal and occipital tumors, respectively. 36 patients (92.3%) received a gross total resection (GTR) whereas 3 patients (7.7%) had a partial resection. After resection, 27 patients (69.2%) underwent combined RT and TMZ [2], 9 (17.9%) RT and 3 (7.7%) TMZ alone. Confirmed MGMT Promoter-methylation-status was achieved in 20 (51.3%). In 9 patients (23.1%) the MGMT Promoter was not methylated, in 10 Patients (25.6%) the methylation-status remained unknown. IDH1/2-mutation-status was wild-type in 36 patients (92.3%), mutated in 0 (0%), unknown in 3 (7.7%). Postoperative complications were sparse; hypertonia was the most common comorbidity, being present in 16 patients (41%).

When comparing the groups of patients that underwent a single resection with those who received a re-resection, no significant differences were observed. Local recurrence was dominant in both groups with 38 patients respectively (97.4%). Postsurgical complications were also rare; hypertonia was the most frequent comorbidity (46.2%).

Impact of GBM re-resection in elderly patients

In 39 patients who suffered a GBM recurrence a re-resection was performed. The univariate Cox-regression analysis revealed initially a significant and clear prolongation of OS in the group of patients who underwent a second resection (16.5 months; CI 95% 13.97–26.2) versus patients from the matched group who only had one surgery (9.04 months; CI 95% 5.79–12.4) (HR: 0.5 95% CI 0.29–0.84, $p \leq 0.0097$) (Fig. 2a). However, a classical Cox model is not able to measure the actual effect of the re-resection as patients who received a second surgery required a longer survival to reach the time point of the second surgery. This effect is manifested by a plateau phase in the survival curve at the beginning (Fig. 2a). In order to analyze whether patients actually benefited from a second resection, we implemented time of resection as a time-dependent co-variable in order to reduce statistical bias (Fig. 2b). A clear increase in the OS in the group of elderly patients who underwent a second resection was confirmed (HR 0.75 95% CI 0.62–0.85, $p \leq 0.03$). On the other hand, patients who received an adjuvant combined RT and TMZ [2] did not exhibit a longer OS than patients who were treated either with RT or TMZ, as shown in the multivariate cox-regression analysis in Fig. 2b. Furthermore, the thorough analysis of the hazard ratio (HR) for treatment comparison indicated that neither GBM localization nor adjuvant therapy affected OS in our patient cohort (Fig. 2c). Other variables such as sex, age or KPS were also not significant. In contrast, re-resection turned out to be the only variable which showed a significal survival benefit when compared to patients that were only operated once (HR 4.6, 2.9–7.2, < 0.001).

Discussion

The adequate management of GBM in elderly patients has always been controversial. Elderly patients are susceptible to a greater risk of unfavorable outcomes because of medical comorbidities, which often leads to under treatment [5]. A correlation between an increasing OS with greater extent of resection, regardless of age, was previously demonstrated in several studies [12, 16, 17]. However, the benefit of a re-resection in the OS of elderly patients remained poorly explored. In order to address this question, our research focused on investigating the impact of surgery at GBM recurrence. We introduced an elaborate statistical approach that attempts to minimize bias caused by the retrospective nature of the study [18]. The control cohort was selected based on a nonparametric computational model [19] including all survival relevant co-variables. Special attention was paid to clinically relevant events and outcome determining parameters such as age, MGMT methylation status and first line therapy. One of the most serious flaws in the interpretation of survival statistics occurs due to an unbalanced cohort that inevitably arises from selection in retrospective studies [19]. Particularly in the evaluation of second-line therapies, patients are naturally selected by the fact that they are candidates for a second therapy. So far, these challenges, especially in the interpretation of the effect recurrent surgeries, have been discussed

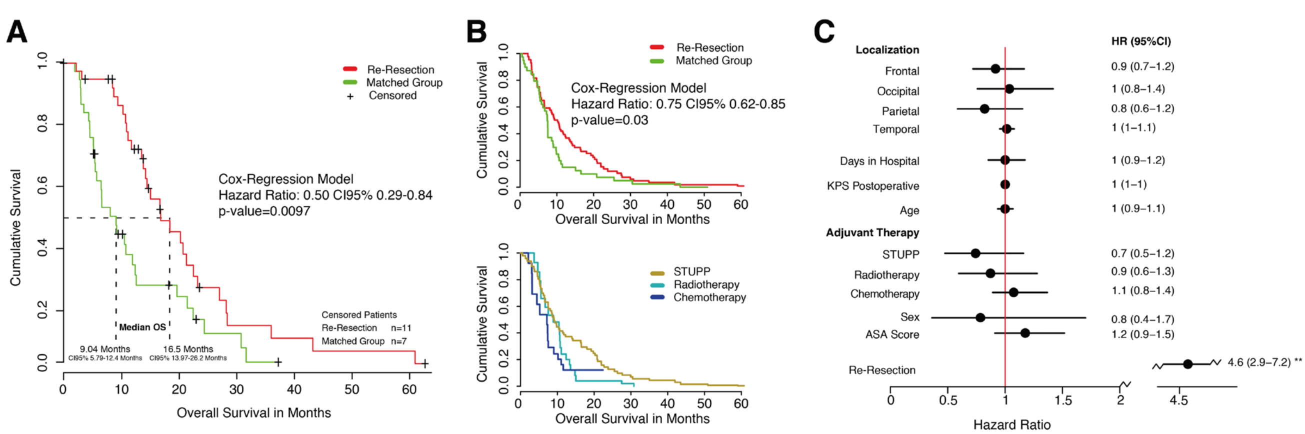

Fig. 2 Statistical Analysis of the OS. **a** Comparison of the OS in patients who underwent surgery at GBM recurrence (red) with the matched cohort (green). Observe the significant increase in the OS for patients undergoing a second resection. **b** Cox-regression model including re-resection as a time-dependent variable. There is no significant difference between RT, CT or combined therapy. **c** Analysis of the hazard ratio showing that the only significant factor regarding OS is re-resection

several times in the literature and the use of improved statistical models is nowadays recommended [18]. In our work, we attempted to both match the clinical features and to use a time-dependent cox-regression survival estimation in order to minimize statistical flaws in the best possible way. Through this approach we determined an improved post recurrence survival of at least 7 months for patients who underwent a re-resection at GBM recurrence. Compared to other published studies, our predicted survival benefit remained relatively low [19–21], although in those studies several prognostic markers such as KPS, extent of resection and tumor localization were not adequately balanced. This leads to unclear significance of the results and to biased conclusions. The descriptive evaluation of our clinical data revealed no significant differences regarding KPS and extent of resection due to our pseudo-randomized cohort.

In addition, our study addressed a small subset of GBM patients, meaning that a limited number of patients could be enrolled, which translated in a limited power of our presented work. For instance, in contrast with other works, our re-resected cohort contains 92.3% of GTR at recurrent stage, which is above the average percentage of GTR. This large percentage of GTR is due to the selection of patients who on the one hand have relatively small recurrent tumors and on the other are in excellent clinical condition. Although we aimed to optimize our model, our work is also limited by the retrospective character. Therefore, we emphasize that randomized prospective trials are necessary to improve the meaningfulness of conclusions.

Our study generates evidence and concludes that elderly patients would benefit from a re-resection of their GBM recurrence. We did not observe relevant postoperative complications or a significant deterioration of KPS in our group of patients. The functional outcome is also to be taken into consideration when performing a tumor resection: it is well known that partial resections are correlated with reduced postoperative morbidity but also with a reduced or not significantly improved OS [22]. However, our study did not include many patients with GBM in eloquent areas. Therefore, future research needs to assess the OS and the complication rate of patients receiving surgery for GBM recurrence in eloquent areas. Prospective studies need to be carried out analyzing the effect of surgery at recurrence combined with postoperative treatment with adjuvant RT and/or TMZ. Finally, the effects of new therapies such as immunotherapy [23] need to be taken into account and also be prospectively in order to ensure the optimal improvement of OS.

Funding This study was funded by the German Cancer Society (SGTII) and the Müller-Fahnenberg Stiftung.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Laperriere N, Weller M, Stupp R, Perry JR, Brandes AA, Wick W et al (2013) Optimal management of elderly patients with glioblastoma. Cancer Treat Rev 39:350–357
2. Stupp R, Taillibert S, Kanner A et al (2017) Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. JAMA 318(23):2306–2316. https://doi.org/10.1001/jama.2017.18718
3. Minniti G, De Sanctis V, Muni R et al (2009) Hypofractionated radiotherapy followed by adjuvant chemotherapy with temozolomide in elderly patients with glioblastoma. J Neuro-Oncol 91:95–100
4. Tanaka S, Meyer FB, Buckner JC, Uhm JH, Yan ES, Parney IF (2013) Presentation, management, and outcome of newly diagnosed glioblastoma in elderly patients. J Neurosurg 118(4):786–798
5. Heiland DH, Haaker G, Watzlawick R et al (2018) One decade of glioblastoma mulforme surgery in 342 elderly patients: what have we learned? J Neurooncol. https://doi.org/10.1007/s11060-018-2964-8
6. Stupp R, Mason WP, van den Bent MJ et al (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352:987–996
7. Jordan JT, Gerstner ER, Batchelor TT, Cahill DP, Plotkin SR (2016) Glioblastoma care in the elderly. Cancer 122:189–197
8. Malmström A, Grønberg BH, Marosi C et al (2012) Temozolamide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomized, phase 3 trial. Lancet Oncol 13(9):916–926
9. Wick W, Platten M, Meisner C et al (2012) Temozolamide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. Lancet Oncol 3(7):707–715
10. Sughrue ME, Sheean T, Bonney PA, Maurer A J & Teo C. (2015) Aggressive repeat surgery for focally recurrent primary glioblastoma: outcomes and theoretical framework. Neurosurg Focus FOC 38(3):E11. Accessed Oct 29, 2018. https://thejns.org/view/journals/neurosurg-focus/38/3/article-pE11.xml
11. Sanai N, Berger MS (2008) Glioma extent of resection and its impact on patient outcome. Neurosurgery 62:753–764
12. Karsy M, Yoon N, Boettcher L et al (2018) Surgical treatment of glioblastoma in the elderly: the impact of complications. J Neurooncol 138:123. https://doi.org/10.1007/s11060-018-2777-9
13. Chaichana KL, Garzon-Muvdi T, Parker S et al (2011) Supratentorial glioblastoma multiforme: the role of surgical resection versus biopsy among older patients. Ann Surg Oncol 18:239–245
14. Ewelt C, Goeppert M, Rapp M, Steiger HJ, Stummer W, Sabel M (2011) Glioblastoma multiforme of the elderly: the prognostic effect of resection on survival. J Neurooncol 103:611–618
15. Perry JR, Laperriere N, O'Callaghan CJ et al (2017) Short-course radiation plus temozolomide in elderly patients with glioblastoma. N Engl J Med 376:1027–1037
16. Harris G, Jayamanne D, Wheeler H et al (2017) Survival outcomes of elderly patients with glioblastoma multiforme in their 75th year or older treated with adjuvant therapy. Int J Radiat Oncol Biol Phys 98:802–810

17. Lacroix M, Abi D, Fourney DR et al (2001) A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. J Neurosurg 95:190–198
18. Slutsky DJ (2013) Statistical errors in clinical studies. J Wrist Surg 2(4):285–287. https://doi.org/10.1055/s-0033-1359421
19. Colson KE, Rudolph KE, Zimmerman SC, et al (2016) Optimizing matching and analysis combinations for estimating causal effects. Sci Rep 6:23222. https://doi.org/10.1038/srep23222
20. Goldman DA, Hovinga K, Reiner AS, Esquenazi Y, Tabar V, Panageas KS (2018) The relationship between repeat resection and overall survival in patients with glioblastoma: a time-dependent analysis. J Neurosurg 129(5):1231–1239. https://doi.org/10.3171/2017.6.JNS17393
21. Chaichana KLKK, Chaichana KLKK, Olivi A, Weingart JD, Bennett R, Brem H, Quinones A (2011) Surgical outcomes for older patients with glioblastoma multiforme: preoperative factors associated with decreased survival. Clinical article. J Neurosurg 114:587–594
22. Wann A, Tully PA, Barnes EH et al (2018) Outcomes after second surgery for recurrent glioblastoma: a retrospective case-control study. J Neurooncol 137:409
23. Reardon DA, Omuro A, Brandes A, et al. (2017) OS10.3 randomized phase 3 study evaluating the efficacy and safety of nivolumab vs bevacizumab in patients with recurrent glioblastoma: checkmate 143. Neuro-Oncology 19(3):21

Affiliations

Mateo Tomas Fariña Nuñez[1,2,7] · Pamela Franco[1,2,7] · Debora Cipriani[1,2,7] · Nicolas Neidert[1,2,7] · Simon P. Behringer[1,2,7] · Irina Mader[3,4] · Daniel Delev[5] · Christian Fung[2,7] · Jürgen Beck[2,7] · Roman Sankowski[6,7] · Nils Henrik Nicolay[7,8] · Dieter Henrik Heiland[1,2,7] · Oliver Schnell[1,2,7]

[1] Translational NeuroOncology Research Group, Medical Center, University of Freiburg, Freiburg, Germany

[2] Department of Neurosurgery, Medical Center, University of Freiburg, Breisacher Straße 64, 79106 Freiburg, Germany

[3] Department of Neuroradiology, Medical Center, University of Freiburg, Freiburg, Germany

[4] Clinic for Neuropediatrics and Neurorehabilitation, Epilepsy Center for Children and Adolescents, Schön Klinik, Vogtareuth, Germany

[5] Department of Neurosurgery, University of Aachen, Aachen, Germany

[6] Institute of Neuropathology, Medical Center, University of Freiburg, Freiburg, Germany

[7] Medical Faculty, University of Freiburg, Freiburg, Germany

[8] Department of Radiation Oncology, Medical Center, University of Freiburg, Freiburg, Germany