Glioma case series

2023

Retrospective data from patients imaged between March 2012 and February 2016 were analyzed by grouping them as IDH-TERT subgroups and by IDH and TERT mutation status. DTI variables in the IDH-TERT subgroups were first identified by the Kruskal-Wallis test, followed by Dunn-Šidák multiple comparisons with Bonferroni correction. IDH and TERT mutations were compared with the Mann–Whitney U test. Classification by thresholding was tested using receiver operating characteristic analysis.

Of 170 patients, 70 patients (mean age, 43.73 [SD, 15.32] years; 40 men) were included. Whole-brain normal-appearing white matter fractional anisotropy (FA) and relative anisotropy (RA) (P = .002) were significantly higher and the contralateral-ipsilateral hemispheric differences, ΔFA and ΔRA, (P < .001) were significantly lower in IDHonly patients compared with TERTonly, with a higher whole-brain normal-appearing white matter FA and RA (P = .01) and ΔFA and ΔRA (P = .002) compared to double positive patients. Whole-brain normal-appearing white matter ADC (P = .02), RD (P = .001), λ2 (P = .001), and λ3 (P = .001) were higher in IDH wild-type. Whole-brain normal-appearing white matter λ1 (AD) (P = .003), FA (P < .001), and RA (P = .003) were higher, but Δλ1 (P = .002), ΔFA, and ΔRA (P < .001) were lower in IDH mutant versus IDH wild-type. ΔFA (P = .01) and ΔRA (P = .02) were significantly higher in TERT mutant versus TERT wild-type.

Axial and nonaxial diffusivities, anisotropy indices in the normal-appearing white matter and their interhemispheric differences demonstrated microstructural differences between IDH and TERT mutations, with the potential for classification methods [1].

All adult patients with histologically proven diffuse (WHO°II) or anaplastic (WHO°III) glioma who underwent their first surgery at the authors' institution between 2010 and 2019 were retrospectively included. Tumor volume on pre- and postoperative MRI scans was determined. Clinical and routine neuropathological data were gained from patients' charts. If IDH1, ATRX, and EGFR were not routinely assessed, they were re-determined.

Results: Out of 161 patients included, 23 (14%) were diagnosed as incidental findings. The main reasons for obtaining MRI were: headache(n = 12), trauma(n = 2), MRI indicated by other departments(n = 7), staging examination for cancer(n = 1), and volunteering for MRI sequence testing(n = 1). The asymptomatic patients were significantly younger with a median age of 38 years (IqR28-48) vs. 50 years (IqR38-61), p = 0.011. Incidental LGG showed significantly lower preoperative tumor volumes in T1 CE (p = 0.008), FLAIR (p = 0.038), and DWI (p = 0.028). Incidental LGG demonstrated a significantly lower incidence of anaplasia (p = 0.004) and lower expression of MIB-1 (p = 0.008) compared to sLGG. IDH1-mutation was significantly more common in iLGG (p = 0.024). Incidental LGG showed a significantly longer OS (mean 212 vs. 70 months, p = 0.005) and PFS (mean 201 vs. 61 months, p = 0.001) compared to sLGG.

The study is the first to depict a significant difference in molecular characteristics between iLGG and sLGG. The findings of this study confirmed and extended the results of previous studies showing a better outcome and more favorable radiological, volumetric, and neuropathological features of iLGG [2].

121 patients with pretreated gliomas of WHO CNS grades 3 or 4, structural MRI, O-(2-[18F]fluoroethyl)-L-tyrosine (FET) PET, resting-state functional MRI (rs-fMRI) and self-reported HRQoL questionnaires (EORTC QLQ-C30/BN20) were obtained. Resection cavities, T1-enhancing lesions, T2/FLAIR hyperintensities, and lesions with pathologically increased FET uptake were delineated. Effects of tumor lateralization, involvement of white matter tracts or resting-state network nodes by different types of lesions, and within-network rs-fMRI connectivity were analyzed in terms of their interaction with HRQoL scores.

Results: Right hemisphere gliomas were associated with significantly less favorable outcomes in physical, role, emotional, and social functioning, compared with left-sided tumors. Most functional HRQoL scores correlated significantly with right-sided white-matter tract involvement by T2/FLAIR hyperintensities and with loss of within-network functional connectivity of right-sided nodes. Tumors of the left hemisphere caused significantly more communication deficits.

In pretreated high-grade gliomas, right hemisphere lesions are associated with reduced HRQoL scores in most functional domains except communication ability, compared to tumors of the left hemisphere. These relationships are mainly observed for T2/FLAIR lesions involving structural and functional networks in the right hemisphere. The data suggest that sparing the right hemisphere from treatment-related tissue damage may improve HRQoL in glioma patients [3)]

Fourteen patients with suspected glioma were enrolled. Histopathological confirmation was available in 12 patients. IDH mutation was confirmed in 9 out of 12 cases and 3 cases were characterized as IDH wildtype. SLOW-EPSI at 7 T showed the highest accuracy for IDH-status prediction (91.7% accuracy, 11 of the 12 predictions correct with 1 false negative case). At 7 T, MEGA-CSI had an accuracy of 58.3% and MEGA-SVS had an accuracy of 75%. At 3 T, MEGA-CSI showed an accuracy of 63.6% and MEGA-SVS of 33.3%. The co-edited cystathionine was detected in 2 out of 3 oligodendroglioma cases with 1p/19q codeletion.

Depending on the pulse sequence, spectral editing can be a powerful tool for the noninvasive determination of the IDH status. SLOW-editing EPSI sequence is the preferable pulse sequence when used at 7 T for IDH-status characterization [4)].

2022

Zhang et al. introduced an individual-level structural anomaly detection method for glioma patients and proposed several abnormality indexes to depict individual atrophy patterns. Forty-five patients with a glioma in the frontal lobe and fifty-one age-matched healthy controls participated in the study. Individual structural abnormality maps (SAM) were generated using patients' preoperative T1 images, by calculating the degree of deviation of voxel volume in each patient with the normative model built from healthy controls. Based on SAM, a series of individual abnormality indexes were computed, and their relationship with glioma characteristics was explored. The results demonstrated that glioma patients showed unique non-tumoral atrophy patterns with overlapping atrophy regions mainly located in the hippocampus, parahippocampus, amygdala, insula, middle temporal gyrus and inferior temporal gyrus, which are closely related to the human cognitive functions. The abnormality indexes were associated with several molecular biomarkers including isocitrate dehydrogenase (IDH)

mutation, 1p/19q co-deletion and telomerase reverse transcriptase (TERT) promoter mutation. The study provides an effective way to access the individual-level non-tumoral structural abnormalities in glioma patients, which has the potential to significantly improve individualized precision medicine [5].

2021

Muster et al. retrospectively reviewed single-institution prospectively collected brain mapping data of patients with dominant hemisphere gliomas. Comparisons of stimulation threshold were made using t-tests and ANOVAs. Associations between oncologic factors and stimulation threshold were made using multivariate regressions. The association between stimulation current and the number of positive sites was made using a Poisson model.

Of the 586 patients included in the study, Stimulation-induced seizure (SIS) occurred in 3.92% and the rate of SIS events differed by cortical location (frontal 8.5%, insular 1.6%, parietal 1.3%, and temporal 2.8%; P = .009). Stimulation current was lower when mapping the frontal cortex (P = .002). Stimulation current was not associated with tumor plus peritumoral edema volume, world health organization) (WHO grade, histology, or isocitrate dehydrogenase (IDH) mutation status but was associated with tumor volume within the frontal lobe (P = .018). Stimulation current was not associated with the number of positive sites identified during ECS mapping (P = .118).

Stimulation-induced seizures are rare but serious events during electrocortical stimulation (ECS) mapping. SISs are most common when mapping the frontal lobe. Greater stimulation current is not associated with the identification of more cortical functional sites during glioma surgery [6].

2020

Senft et al. assessed neuro-oncological and functional outcomes of patients with World Health Organization grade 2 and World Health Organization grade 3 gliomas undergoing surgery between 2012 and 2018. All patients underwent routine follow-up and adjuvant treatment. Treatment and survival parameters were collected prospectively. Repercussions of the disease on the patients' professional status, socio-economic situation, and neurocognitive function were evaluated retrospectively with questionnaires.

They analyzed data of 58 patients with gliomas (WHO II: 9; III: 49). Median patient age was 35.8 years (range 21-63 years). Awake surgery techniques were applied in 32 patients (55.2%). Gross total and subtotal tumor resections were achieved in 33 (56.9%) and 17 (29.3%) patients, respectively, whereas in 8 patients (13.8%) resection had to remain partial. Most patients (n = 46; 79.3%) received adjuvant treatment. Median follow up was 43.8 months (range 11-82 months). After treatment 41 patients (70.7%) were able to resume a working life. Median time until returning to work was 8.0 months (range 0.2-22.0 months). To be younger than 40 at the time of the surgery was associated with a higher probability to return to work ($p < .001$). Multivariable regression analysis showed that patient age < 40 years as well as occupational group and self-reported fatigue were factors independently associated with the ability to return to work.

The ability to resume professional activities following brain tumor surgery is an important patient-oriented outcome parameter. They found that the majority of patients with gliomas were able to return to work following surgical and adjuvant treatment. Preservation of neurological function is of utmost relevance for individual patients´ quality of life [7].

A total of 124 Chinese patients with gliomas were enrolled to study the frequencies of mutations in isocitrate dehydrogenase (IDH) and telomerase reverse transcriptase promoter (TERTp). Among the 124 patients, 59 patients were enrolled to study the classification of gliomas based on mutations in IDH and TERTp. Isocitrate dehydrogenase mutations are positively correlated with a good prognosis but mutations in TERTp cannot predict prognoses independently. The combined analysis of the mutations of IDH and TERTp can predict the prognosis more accurately. Patients with IDH and TERTp glioma mutations have the best prognosis, followed by only IDH mutation patients and only TERTp mutation patients, which have the worst prognosis. IDH and TERTp mutations occur frequently in males, younger patients or lower-grade patients. In contrast, only TERTp mutations occur frequently in females, older patients or higher-grade patients.

Patients with IDH and TERTp glioma mutations have the best prognosis, and only IDH mutation patients and only TERTp mutation patients have the worst prognosis. Moreover, the molecular classification of gliomas by mutations of IDH and TERTp is not suitable for pediatric patients [8)]

2019

Michiwaki et al. evaluated 234 glioma patients according to the updated WHO classification. Isocitrate dehydrogenase (IDH), H3F3A, BRAF hotspot mutations, TERT promotor mutation, and chromosome 1p/19q co-deletion were examined. RE, non-RE, GdE, and IC were evaluated as significant neuroimaging findings. Kaplan-Meier analyses were performed to evaluate overall survival (OS) and the correlations of prognostic factors were evaluated by log-rank tests. Univariate and multivariate analyses were performed to detect prognostic factors for OS.

A total of 207 patients were eligible. In 110 patients presenting RE, 102 (93%) were glioblastoma (Glioblastoma), IDH-wild type. In 97 patients without RE, presence of GdE or IC were not significantly different between IDH-mutant and -wild type tumors, whereas presence of GdE was a significant indicator of higher WHO grades. IC was the only significant finding for 1p/19q co-deleted tumors. TERT promoter mutation was observed in 7/17 patients with diffuse astrocytic glioma, IDH-wild type; recently-defined as “molecular Glioblastoma.” IC, RE, and GdE were observed with lower prevalence in molecular Glioblastomas. While presence of RE, GdE, and absence of IC were significant factors of OS in overall cohort, presence of GdE was not significant in OS in cases without RE, and IDH-mutant tumors. IC was a significant predictor of favorable OS in cases without RE and IDH-wild type tumors. Multivariate analysis also validated these findings.

GdE alone is not a significant predictor of IDH mutation status, but the pattern of enhancement is a significant predictor with RE demonstrating high sensitivity and specificity for Glioblastoma, IDH-wild type. Predicting “molecular Glioblastoma” by conventional neuroimaging is difficult. Moreover, GdE is not a significant factor of survival analyzed with pattern of enhancement or molecular stratifications. IC is an important radiographic finding for predicting molecular diagnosis and survival in glioma patients [9)].

2016

From 2012 to 2015, 94 Czech patients with primary brain tumors were enrolled into the study. The

IDH1/2 mutation was detected by denaturing capillary electrophores. The methylation status of the MGMT gene and other 46 genes was revealed by MS-MLPA. In all 94 patients, the clinical data were correlated with molecular markers by Kaplan Meier analyses and Cox regression model. The MGMT promoter methylation status was established and compared to clinical data. In our study eight different probes were used to elucidate the MGMT methylation status; hypermethylation was proclaimed if four and more probes were positive. This 3 : 5 ratio was tested and confirmed by Kaplan-Meier and Cox analyses. The study confirmed the importance of the IDH1/2 mutation and hypermethylation of the MGMT gene promoter being present in tumour tissue. Both markers are independent positive survival predictors; in the Cox model the IDH hazard ratio was 0.10 and in the case of MGMT methylation it reached 0.32. The methylation analysis of the panel of additional 46 genes did not reveal any other significant epigenetic markers; none of the candidate genes have been confirmed in the Cox regression analyses as an independent prognostic factor [10].

1)
Halilibrahimoğlu H, Polat K, Keskin S, Genç O, Aslan O, Öztürk-Işık E, Yakıcıer C, Danyeli AE, Pamir MN, Özduman K, Dinçer A, Özcan A. Associating IDH and TERT Mutations in Glioma with Diffusion Anisotropy in Normal-Appearing White Matter. AJNR Am J Neuroradiol. 2023 Apr 27. doi: 10.3174/ajnr.A7855. Epub ahead of print. PMID: 37105678.
2)
Demetz M, Krigers A, Moser P, Kerschbaumer J, Thomé C, Freyschlag CF. Same but different. Incidental and symptomatic lower grade gliomas show differences in molecular features and survival. J Neurooncol. 2023 Apr 12. doi: 10.1007/s11060-023-04301-x. Epub ahead of print. PMID: 37043120.
3)
Heinzel A, Mottaghy FM, Filss C, Stoffels G, Lohmann P, Friedrich M, Shah NJ, Caspers S, Lucas CW, Ruge MI, Galldiks N, Fink GR, Langen KJ, Kocher M. The impact of brain lesions on health-related quality of life in patients with WHO CNS grade 3 or 4 glioma: a lesion-function and resting-state fMRI analysis. J Neurooncol. 2023 Feb 7. doi: 10.1007/s11060-023-04254-1. Epub ahead of print. PMID: 36750534.
4)
Weng G, Ermiş E, Maragkou T, Krcek R, Reinhardt P, Zubak I, Schucht P, Wiest R, Slotboom J, Radojewski P. Accurate prediction of isocitrate dehydrogenase -mutation status of gliomas using SLOW-editing magnetic resonance spectroscopic imaging at 7 T MR. Neurooncol Adv. 2023 Jan 3;5(1):vdad001. doi: 10.1093/noajnl/vdad001. PMID: 36875625; PMCID: PMC9977233.
5)
Zhang G, Zhang X, Huang H, Wang Y, Li H, Duan Y, Chen H, Liu Y, Jing B, Tie Y, Lin S. Probing individual-level structural atrophy in frontal glioma patients. Neurosurg Rev. 2022 May 4. doi: 10.1007/s10143-022-01800-9. Epub ahead of print. PMID: 35508819.
6)
Muster RH, Young JS, Woo PYM, Morshed RA, Warrier G, Kakaizada S, Molinaro AM, Berger MS, Hervey-Jumper SL. The Relationship Between Stimulation Current and Functional Site Localization During Brain Mapping. Neurosurgery. 2021 May 13;88(6):1043-1050. doi: 10.1093/neuros/nyaa364. PMID: 33289525; PMCID: PMC8117445.
7)
Senft C, Behrens M, Lortz I, Wenger K, Filipski K, Seifert V, Forster MT. The ability to return to work: a patient-centered outcome parameter following glioma surgery. J Neurooncol. 2020 Sep 22. doi: 10.1007/s11060-020-03609-2. Epub ahead of print. PMID: 32960402.
8)
Qu CX, Ji HM, Shi XC, Bi H, Zhai LQ, Han DW. Characteristics of the isocitrate dehydrogenase gene and telomerase reverse transcriptase promoter mutations in gliomas in Chinese patients. Brain Behav. 2020 Mar 8:e01583. doi: 10.1002/brb3.1583. [Epub ahead of print] PubMed PMID: 32146731.
9)
Michiwaki Y, Hata N, Mizoguchi M, Hiwatashi A, Kuga D, Hatae R, Akagi Y, Amemiya T, Fujioka Y, Togao O, Suzuki SO, Yoshimoto K, Iwaki T, Iihara K. Relevance of calcification and contrast

enhancement pattern for molecular diagnosis and survival prediction of gliomas based on the 2016 World Health Organization Classification. Clin Neurol Neurosurg. 2019 Oct 12;187:105556. doi: 10.1016/j.clineuro.2019.105556. [Epub ahead of print] PubMed PMID: 31639630.

10) Kramář F, Minárik M, Benešová L, Halková T, Netuka D, Bradáč O, Beneš V. IDH1/2 Mutation and MGMT Promoter Methylation - the Relevant Survival Predictors in Czech Patients with Brain Gliomas. Folia Biol (Praha). 2016;62(5):194-202. PubMed PMID: 27978414.