Glioblastoma case series

2023

Data of 47 patients with newly diagnosed right cerebral hemispheric GBMs were analyzed. All patients were assessed preoperatively and 3 months postoperatively to determine KPS and brain function. To determine tumor location related to the postoperative KPS scores, we used voxel-based lesion-symptom mapping (VLSM). The patients were divided into two groups (involvement and non-involvement groups) based on whether their lesion involved a significant region identified by VLSM. We then compared functional factors and prognosis between the groups using the chi-squared and log-rank tests, respectively.

The KPS score significantly decreased after surgery compared to that preoperatively measured ($p = 0.023$). VLSM revealed that tumors in the white matter of the temporoparietal junction (WM-TPJ) caused a significant decline in the KPS score at three months postoperatively. The patients in the involvement group had a higher probability of impaired attention, visuospatial cognition, emotion recognition, and visual field than did those in the non-involvement group. In addition, tumors in the WM-TPJ were associated with shorter progression-free survival and overall survival ($p = 0.039$ and 0.023, respectively).

Glioblastomas involving the right white matter of the temporoparietal junction are more likely to result in poor postoperative KPS scores and prognoses. Impairments of several kinds of brain functions caused by tumor invasion to the WM-TPJ may be associated with lower KPS scores [1)].

In the study by Weller et al., the researchers aimed to assess the treatment benefit of bevacizumab in a specific subgroup of patients with glioblastoma, namely those with MGMT unmethylated tumors. They conducted their analysis as part of the GLARIUS trial (NCT00967330), which involved 123 patients. The evaluation of the treatment's effectiveness was based on different gene expression subtypes in pretreatment tumor samples.

To carry out their analysis, the researchers utilized several statistical methods, including Kaplan-Meier analyses, log-rank tests, and Cox regression models. These methods are commonly used in medical research to examine survival outcomes and identify potential factors that influence those outcomes.

The results of their analysis revealed that bevacizumab had a significant advantage in terms of progression-free survival (PFS) for patients with a specific subtype of glioblastoma known as proneural IDH wild-type tumors. Specifically, patients receiving bevacizumab had a longer PFS (10.4 months) compared to those who did not (6.0 months), and this difference was statistically significant ($p = 0.002$). However, when it came to overall survival (OS), there was no significant advantage associated with bevacizumab treatment. Patients who received bevacizumab had a median OS of 16.4 months, while those who did not had a median OS of 17.4 months, and this difference was not statistically significant ($p = 0.6$).

The researchers also conducted a multivariable analysis, which involved adjusting for various prognostic factors that could influence OS. This analysis further confirmed that there was no significant OS advantage from bevacizumab treatment (hazard ratio, 1.05, 95% CI, 0.42 to 2.64; $p = 0.14$). Additionally, they examined whether the subtype of glioblastoma (proneural) interacted with

the treatment arm, and the results showed no significant interaction (p = 0.15). In other words, the subtype of glioblastoma did not significantly influence the treatment's effect on OS.

To validate their findings, the researchers also conducted similar analyses based on different tumor subgroups using the Verhaak classifier, and the results consistently showed that there was no differential OS benefit from first-line bevacizumab treatment in the GLARIUS trial.

In summary, the study by Weller et al. demonstrated that while bevacizumab was associated with a significant advantage in terms of progression-free survival for a specific subtype of glioblastoma (proneural IDH wild-type tumors), it did not confer a significant overall survival benefit in this patient population. These findings were consistent across different analyses and subgroups, highlighting the complexities of treatment response in glioblastoma patients with varying genetic profiles [2)].

Salvalaggio et al. examined two Groups of Patients: The first group, called the “discovery cohort,” included 112 patients from Italy who had surgery between February 2015 and November 2020. The second group, known as the “replicative cohort,” included 70 patients from Germany who had surgery between September 2012 and November 2015.

What They Measured: The researchers were interested in something called “white matter tracts” in the patients' brains. They measured how dense or crowded these tracts were in the area where the GBM was located.

Main Findings:

In the first group (discovery cohort), they found that the density of these white matter tracts was related to how long patients lived after surgery. When the tracts were less dense, patients tended to live longer.

This relationship between white matter tract density and survival was stronger and more consistent compared to other factors that are commonly used to predict how GBM patients will do, like age, performance status, a specific type of DNA change (O6-methylguanine-DNA methyltransferase methylation), and how much of the tumor was removed during surgery. They confirmed these findings in the second group (replicative cohort), which makes the results more reliable. Using the density of white matter tracts, they were able to predict whether a patient would have a higher or lower chance of surviving for at least 18 or 24 months after surgery with a high level of accuracy. Conclusion: This study suggests that the density of white matter tracts in the area around the GBM may be a useful predictor of how long patients with GBM will live after surgery. It could be valuable in clinical trials and medical practice to help doctors make decisions about treatment and prognosis.

In simple terms, the study found that the structure of certain brain pathways is related to how long patients with brain cancer live after surgery. This could be a helpful tool for doctors when treating these patients. [3)].

The data of patients who presented at the university hospital between January 2009 and January 2019 with a confirmed diagnosis of glioblastoma multiforme at the time of diagnosis were analyzed retrospectively. Temporal muscle thickness and temporal muscle area (TMA) were measured retrospectively from preoperative MRIs of patients diagnosed with GBM. Due to the small number of patients and the failure to determine a cut-off value with acceptable sensitivity and specificity using

ROC analysis, the median values were chosen as the cut-off value. The patients were basically divided into two according to their median temporal muscle thickness (TMT) (6.6 mm) or TMA (452 mm2) values, and survival analysis was performed with the Kaplan-Meier analysis.

The median TMT value was 6.6 mm, and the median TMA value was 452 mm2. The median overall survival (OS) was calculated as 25.8 months in patients with TMT < 6.6 mm, and 15.8 months in patients with TMT ≥ 6.6 mm (p = 0.29). The median overall survival (OS) of patients with TMA < 452mm2 was 26.3 months, and the group with TMA ≥ 452mm2 was 14.6 months (p = 0.06). The median disease-free survival was 18.3 months (%95 CI: 13.2-23.4) in patients with TMT < 6.6mm, while mDFS was 10.9 (%95 CI: 8.0-13.8) months in patients with TMT ≥ 6.6mm (p = 0.21). The median disease-free survival was found to be 21.0 months (%95 CI: 15.8-26.1) in patients with TMA < 452 mm2 and 10.5 months (%95 CI: 7.8-13.2) in patients with TMA ≥ 452 mm2 (p = 0.018).

No association could be demonstrated between temporal muscle thickness and temporal muscle area and overall survival of glioblastoma patients. In addition, the median disease-free survival was found to be longer in patients with low temporal muscle area. There is an unmet need to determine the optimal method of sarcopenia in glioblastoma patients [4].

A total number of 49 patients with glioblastoma and 50 healthy controls were included in the current study. The Genomic DNA was extracted from brain tumor/tissue samples, and after purification assessment, the alleles, and genotypes of rs3025039 and rs2010963 polymorphisms of the VEGF gene were investigated using T-ARMS-PCR.

The “T” allele of rs3025039 was 2.79 times more frequent in GBM patients compared to controls (P=0.01). Moreover, the “CT” genotype was 2.83 times more common among patients (P=0.015), while the “CC” was more frequent in controls (P=0.009). The mean overall survival was significantly different between the three genotypes of rs3025039, with the longest survival time in “CT” genotype (15.10±5.21, P=0.041). Besides, rs2010963 was significantly associated with GBM occurrence, with the “G” allele being 1.96 times more frequent in patients (P=0.01), as well as the “GG” genotype, which was 7.87 times more common in patients (P<0.001).

Polymorphisms of VEGF could potentially play a role in the glioblastoma pathogenesis, as the allele and genotype distributions of rs3025039 and rs2010963 SNPs were significantly associated with glioblastoma occurrence [5].

2022

Three hundred and fifty patients with confirmed primary glioblastoma diagnosed and treated between 2005 and 2019 were selected. To examine the role of glioblastoma reoperation, they intended to create comparable groups, previously excluding all diagnostic biopsies and patients who were not actively treated after the first surgery or at disease progression. Uni- and multivariate Cox proportional hazards regression models were employed, considering reintervention as a time-fixed or time-dependent covariate. The endpoints of the study were overall survival (OS) and PPS.

Results: At progression, 33 patients received a second surgery and 84 were treated with chemotherapy only. Clinical variables were similar among groups. OS, but not PPS, was superior in the reintervention group. Treatment modality had no impact in our multivariate Cox regression models considering OS or PPS as the endpoint.

The association of reoperation with improved prognosis in recurrent glioblastoma is unclear and may be influenced by selection bias. Regardless of our selective indications and high gross total resection rates in second procedures, we could not observe a survival advantage [6].

2021

A retrospective study of surgically treated glioblastomas between March 2018 and November 2019 was performed. Patients with IOUS B-mode and strain elastography was included. After preprocessing, segmentation and extraction of radiomics were performed with LIFEx software. An evaluation of semantic segmentation was carried out using the Dice similarity coefficient (DSC). Using univariate correlations, radiomic features associated with OS were selected. Subsequently, survival analysis was conducted using Cox univariate regression and Kaplan-Meier curves.

Sixteen patients were available for analysis. The DSC revealed excellent agreement for the segmentation of the tumour region. Of the 52 radiomic features, two texture features from B-mode (conventional mean and the grey-level zone length matrix/short-zone low grey-level emphasis [GLZLM_SZLGE]) and one texture feature from strain elastography (grey-level zone length matrix/long-zone high grey-level emphasis [GLZLM_LZHGE]) were significantly associated with OS. After establishing a cut-off point of the statistically significant radiomic features, we allocated patients in high- and low-risk groups. Kaplan-Meier curves revealed significant differences in OS.

IOUS-based quantitative texture analysis in glioblastomas is feasible. Radiomic tumor region characteristics in B-mode and elastography appear to be significantly associated with OS [7].

Retrospective single-institution study included patients with glioblastoma treated by concurrent chemoradiotherapy who had newly developed or enlarging, measurable contrast-enhancing mass. Contrast-enhancing mass was divided into three spatial habitats by K-means clustering of voxel-wise ADC and CBV values. Temporal changes of these habitats between two consecutive examinations prior to the diagnosis of tumor progression or treatment-related change were assessed. Predictors were selected using logistic regression and the performance was measured with an area under the receiver operating characteristics curve (AUC). Spatiotemporal habitats were further analyzed for correlation with the site of tumor progression.

There were 75 patients (mean, 58 years; range, 26-81 years; 43 men) with 48 cases of tumor progression and 39 cases of treatment-related change including 12 patient overlaps at different time points. Three spatial habitats of hypervascular cellular, hypovascular cellular, and nonviable tissue were identified. Increase in the hypervascular cellular (OR 4.55, $p = .002$) and hypovascular cellular habitat (OR 1.22, $p < .001$) was predictive of tumor progression. Combination of spatiotemporal habitats yielded a high diagnostic performance with an AUC of 0.89 (95% CI, 0.87-0.92). An increase in hypovascular cellular habitat predicted the site of tumor progression in 84% [21/25] of cases with tumor progression.

Temporal changes in spatial habitats derived from multiparametric physiologic MRI provided diagnostic value in distinguishing tumor progression from treatment-related change and predicted site of tumor progression in post-treatment glioblastoma [8].

2020

Patients with Glioblastoma who received concurrent LITT and surgical resection at the Department of Neurosurgery, University of Texas MD Anderson Cancer Center, Houston were identified. Patient demographic and clinical information was procured from the University of Texas MD Anderson Cancer Center electronic medical record along with preoperative, postoperative, and 1-month follow-up magnetic resonance imaging (MRI).

Four patients (n = 2 male, n = 2 female) with Glioblastoma IDH wildtype who received combined LITT and surgical resection were identified and analyzed retrospectively. All patients received chemoradiotherapy before the presentation. All but one patient (75%) received resection before the presentation. The median age was 54 years (range: 44-56 years). The median length of hospital stay was 6.5 days (range: 2-47 days). The median extent of combined ablation/resection was 90.4%. One of the four patients experienced complications in the perioperative or immediate follow-up periods. Local recurrence was observed in one patient during the follow-up period.

Malignant gliomas in deep-seated locations or in close proximity to white matter structures are challenging to manage. LITT followed by surgical resection may provide an alternative for tumor debulking that minimizes potential morbidities and extent of residual tumor. Further studies comparing this approach with standard resection techniques are warranted [9].

Laurent et al. queried all patients diagnosed with Glioblastoma who underwent surgical resection at the Lillian S. Wells Department of Neurosurgery, Preston A. Wells Center for Brain Tumor Research, College of Medicine, University of Florida, Gainesville, between January 2011 and May 2017. Pre- and postoperative magnetic resonance imaging were analyzed for EOR. Each chart was reviewed to determine the incidence of PSIs and HACs.

A total of 284 patients met the inclusion criteria. EOR ranged from 39.00 to 100%, with a median of 99.84% and a mean of 95.7%. There were 16 PSI, and 13 HAC, events. There were no significant differences in the rates of PSIs or HACs when compared between patients stratified by gross total resection (EOR ≥ 95%) and subtotal resection (EOR < 95%). The odds of encountering a PSI or HAC were 2.5 times more likely in the subtotal resection group compared to the gross total resection group (P = .58). After adjusting for confounders, the odds of encountering a PSI or HAC in the subtotal resection group were 3.9 times greater than for the gross total resection group (P < .05).

Gross total resection of Glioblastoma is associated with a decreased incidence of patient safety indicators (PSIs) and hospital-acquired conditions (HACs), as compared to subtotal resection [10].

From the nationwide Finnish Cancer Registry, Raj et al. identified all adult (≥ 18 years) patients with histopathological diagnoses of glioblastoma from 2000 to 2013. Five university hospitals (treating all glioblastoma patients in Finland) were classified as high-volume (one hospital), middle-volume (one hospital), and low-volume (three hospitals) based on their annual numbers of cases. We estimated one-year survival rates, estimated median overall survival times, and compared relative excess risk (RER) of death between high, middle, and low-volume hospitals.

A total of 2,045 patients were included. The mean numbers of annually treated patients were 54, 40, and 17 in the high, middle, and low-volume hospitals, respectively. One-year survival rates and

median survival times were higher and longer in the high-volume (39%, 9.3 months) and medium-volume (38%, 8.9 months) hospitals than in the low-volume (32%, 7.8 months) hospitals. RER of death was higher in the low-volume hospitals than in the high-volume hospital (RER = 1.19, 95% CI 1.07-1.32, p = 0.002). There was no difference in RER of death between the high-volume and medium-volume hospitals (p = 0.690).

Higher glioblastoma case volumes were associated with improved survival. Future studies should assess whether this association is due to differences in patient-specific factors or treatment quality [11)].

Between November 2012 and June 2016, all consecutive patients presenting with a suspected glioblastoma in the western region of Sweden were registered in a population-based study. Of the 378 patients, 131 (35%) met the inclusion criteria of the present study by typical radiological features of glioblastoma without histological verification.

The clinical characteristics of the 131 patients (72 men, 59 women) were: age ≥ 75 (n = 99, 76%), performance status according to Eastern Cooperative Oncology Group ≥ 2 (n = 93, 71%), significant comorbidity (n = 65, 50%) and multilobular tumors (n = 90, 69%). The overall median survival rate was 3.6 months. A subgroup of 44 patients (34%) received upfront treatment with temozolomide, with an overall radiological response rate of 34% and a median survival of 6.8 months, compared to 2.7 months for those receiving best supportive care only. Good performance status and temozolomide treatment were statistically significant favorable prognostic factors, while younger age was not.

Thirty-five percent of patients with a radiological diagnosis of glioblastoma in the western region of Sweden region lacked histological diagnosis. Apart from high age and poor performance status, they had more severe comorbidities and extensive tumor spread. Even for this poor prognostic group upfront treatment with temozolomide was shown of benefit in a subgroup of patients. This data illustrate the need of non-invasive diagnostic methods to guide optimal individualized therapy for patients considered too fragile for neurosurgical biopsy [12)].

A total of 115 primary glioblastoma patients were prospectively recruited for surgery and preoperative magnetic resonance imaging. The joint histograms of decomposed anisotropic and isotropic components of DTI were constructed in both contrast-enhancing and nonenhancing tumor regions. Patient survival was analyzed with joint histogram features and relevant clinical factors. The incremental prognostic values of histogram features were assessed using receiver operating characteristic curve analysis. The correlation between the proportion of diffusion patterns and tumor progression rate was tested using Pearson correlation.

They found that joint histogram features were associated with patient survival and improved survival model performance. Specifically, the proportion of nonenhancing tumor subregion with decreased isotropic diffusion and increased anisotropic diffusion was correlated with tumor progression rate ($P = .010$, $r = 0.35$), affected progression-free survival (hazard ratio = 1.08, $P < .001$), and overall survival (hazard ratio = 1.36, $P < .001$) in multivariate models.

Joint histogram features of DTI showed incremental prognostic values over clinical factors for glioblastoma patients. The nonenhancing tumor subregion with decreased isotropic diffusion and increased anisotropic diffusion may indicate a more infiltrative habitat and potential treatment target [13)].

79 patients with Glioblastoma were operated on with Intraoperative magnetic resonance imaging (iMRI). Additional resection was performed if iMRI depicted contrast enhancing tissue suggestive of residual tumor. GTR and extent of tumor resection (EOR) were determined by segmentation and volumetric analysis of the MR images. Surgical site infection (SSI) and the role of intravenous only or intravenous plus intrathecal antibiotics were evaluated. Statistical analysis was performed to detect the sensitivity, specificity, positive predictive value, and negative predictive value of iMRI-guided extended resections. Pearson's two-tailed chi-square test was performed to evaluate the rates of GTR and variables associated with SSI.

GTR was achieved in 59 patients (74.68%). Rate of GTR was 35.44% before iMRI and additional resections ($p < 0.0001$). Mean EOR was 96.27%. Positive predictive value for tumor cells in the additionally resected tissue was 88.6%, negative predictive value was 100%, sensitivity was 100%, and specificity was 70. 6%. Rate of SSIs was 5.06% ($n = 4$). Two superficial SSIs, one subdural empyema and one cerebritis, were seen. SSI rates with parenteral only and additional intrathecal antibiotics were 0% and 8%, respectively ($p = 0.133$).

It is still discussed if the dual use increases the risk of surgical site infections (SSI).Increase of extent of tumor resection using iMRI is evident. SSI rate is within the normal range of neurosurgical procedures. A dual-use iMRI suite is a safe concept [14].

Eighteen Glioblastoma patients were retrospectively analyzed. After completion of therapy, imaging was performed every 3 months. MRI was analyzed at the following time points: after the third and sixth cycle of adjuvant temozolomide chemotherapy, thereafter in 3 month intervals and at recurrence. The number of SWI positive tumor pixels was quantified and compared with progression as defined by the RANO criteria on T2- and contrast-enhanced T1-weighted MRI sequences (T1-CE).

The MRI interval between completion of the sixth chemotherapy cycle and last MRI before progression was 390 ± 292 days. Between the last MRI before progression and at progression a significant increase in SWI positive tumor pixels was observed ($P = .012$), whereas tumor size remained unchanged (RANO T2: $P = .385$; RANO T1-CE: $P = .165$). The number of SWI positive pixels remained unchanged between last MRI before progression until progression ($P = .149$), whereas RANO T2 and T1-CE showed tumor progression (interval 128 ± 69 days).

SWI positive pixel count increases significantly prior to changes in tumor size (RANO). The findings may be explained by microbleeds compatible with stimulation of angiogenesis and possibly serve as an early biomarker of tumor progression [15].

Multi-channel MR image derived texture features, tumor shape, and volumetric features, and patient age were obtained for 163 Glioblastoma patients. In order to assess the impact of tumor shape features on OS prediction, two feature sets, with and without tumor shape features, were created. For the feature set with tumor shape features, the mean prediction error (MPE) was 14.6 days and its 95% confidence interval (CI) was 195.8 days. For the feature set excluding shape features, the MPE was 17.1 days and its 95% CI was observed to be 212.7 days. The coefficient of determination (R2) value obtained for the feature set with shape features was 0.92, while it was 0.90 for the feature set excluding shape features. Although marginal, inclusion of shape features improves OS prediction in

Glioblastoma patients. The proposed OS prediction method using regression provides good accuracy and overcomes the limitations of Glioblastoma OS classification, like choosing data-derived or pre-decided thresholds to define the OS groups. Graphical abstract Two feature sets: with and without tumor shape features were extracted from T1-weighted contrast-enhanced, T2-weighted and FLAIR MRI. These feature sets were analyzed using the Mean Prediction Error (MPE) and its 95% Confidence Interval (CI) obtained from the Bland-Altman plot, along with the coefficient of determination (R2) value to assess the impact of tumor shape features on overall survival prediction of glioblastoma multiforme patients [16)]

Seventy-five patients from 25 to 84 years old (Median age 62 years) with preoperative, immediate postoperative, and preradiotherapy MRI from Toulouse were included. Volumetric measurements were made on each of the three MRI scans and clinical and molecular parameters were collected for each case.

Fifty-four patients (72%) had an early regrowth with a median contrast enhancement volume of 3.61 cm3-range 0.12-71.93 cm3. The median OS was 24 months in patients with no early tumor growth and 17.1 months in those with early tumor regrowth ($p = 0.0024$). In the population with initial complete resection (27 patients), the median OS was 25.3 months (19 patients) in those with no early tumor growth between surgery and radiotherapy compared to 16.3 months (8 patients) in those with tumor regrowth. In multivariate analysis, the initial extent of resection ($p < 0.001$) and the delay between postoperative MRI and preradiotherapy MRI ($p < 0.001$) were significant independent prognostic factors of regrowth and of poorer outcome.

They demonstrated that, in addition to the well known issue of incomplete resection, longer delays between surgery and adjuvant treatment is an independent factors of tumor regrowth and a risk factor of poorer outcomes for the patients. To overcome the delay factor, they suggest shortening the usual time between surgery and radiotherapy [17)].

2018

Data from Glioblastoma extent of resection patients who underwent gross total resection (GTR), subtotal resection (STR), or open biopsy between 2005 and 2014 were retrieved from the Surveillance, Epidemiology, and End Results database in the Seoul National University College of Medicine.

Univariate and multivariate analyses for overall survival (OS) were performed. Between 2005-2009 and 2010-2014, the proportion of GTR and STR performed increased from 41.4 to 42.3% and 33.0 to 37.1%, respectively. EOR only affected OS in the 3 years after diagnosis. Median survival in the GTR ($n = 4155$), STR ($n = 3498$), and open biopsy ($n = 2258$) groups was 17, 13, and 13 months, respectively ($p < .001$). STR showed no significant difference in OS from open biopsy ($p = .33$). GTR increased OS for midline-crossing tumors. Although STR was more frequently performed than GTR for tumors ≥ 6 cm in size, GTR significantly increased the OS rate relative to STR for tumors 6-8 cm in size ($p = .001$). For tumors ≥ 8 cm, STR was comparable to GTR ($p = .61$) and superior to open biopsy ($p = .05$). GTR needs to be performed more frequently for glioblastoma measuring ≥ 6 cm or that have crossed the midline to increase OS. STR was marginally superior to open biopsy when the tumor was ≥ 8 cm [18)].

Pérez-Beteta et al., evaluated the prognostic and predictive value of surface-derived imaging biomarkers obtained from contrast material-enhanced volumetric pretreatment T1 weighted image magnetic resonance sequences in patients with glioblastoma multiforme.

A discovery cohort from five local institutions (165 patients; mean age, 62 years ± 12 [standard deviation]; 43% women and 57% men) and an independent validation cohort (51 patients; mean age, 60 years ± 12; 39% women and 61% men) from The Cancer Imaging Archive with volumetric T1-weighted pretreatment contrast-enhanced MR imaging sequences were included in the study. Clinical variables such as age, treatment, and survival were collected. After tumor segmentation and image processing, tumor surface regularity, measuring how much the tumor surface deviates from a sphere of the same volume, was obtained. Kaplan-Meier, Cox proportional hazards, correlations, and concordance indexes were used to compare variables and patient subgroups.

Surface regularity was a powerful predictor of survival in the discovery (P = .005, hazard ratio [HR] = 1.61) and validation groups (P = .05, HR = 1.84). Multivariate analysis selected age and surface regularity as significant variables in a combined prognostic model (P < .001, HR = 3.05). The model achieved concordance indexes of 0.76 and 0.74 for the discovery and validation cohorts, respectively. Tumor surface regularity was a predictor of survival for patients who underwent complete resection (P = .01, HR = 1.90). Tumors with irregular surfaces did not benefit from total over subtotal resections (P = .57, HR = 1.17), but those with regular surfaces did (P = .004, HR = 2.07).

The surface regularity obtained from high-resolution contrast-enhanced pretreatment volumetric T1-weighted MR images is a predictor of survival in patients with glioblastoma. It may help in classifying patients for surgery [19].

Urhie et al., retrospectively determined the impact of age of diagnosis, number of lesions, the molecular marker O6-methylguanine methyltransferase (MGMT), extent of surgery, and completion of the Stupp protocol on survival among patients treated at West Virginia University Hospitals. They found that an age of diagnosis under 60 years, having the MGMT gene methylated, having a unifocal tumor, receiving GTR, adhering to the Stupp protocol, and undergoing a treatment course of GTR followed by the Stupp protocol significantly increased survival. Lastly, they compared the findings to a pre-Stupp study done in West Virginia in 1996. This comparison showed that although overall median survival has not increased, all interventions involving GTR have resulted in a significantly higher survival [20].

Carroll et al. identified and studied 1,429 AA patients and 12,537 GB patients in the SEER database with lobar tumors. In multivariate Cox proportional hazards analysis, GTR of frontal lobe AA was associated with a ~50% reduction in the risk of death compared to subtotal resection (STR) (HR 0.51, 95% CI 0.36-0.73, p<0.001). This hazard ratio corresponds to a >8 year increase in median overall survival with GTR compared to STR. In contrast, in non-frontal AAs there was no survival difference between GTR and STR (HR 0.79, CI 0.58-1.08, p=0.143). Further, the location-specific survival benefit from GTR in AAs was significant in patients ≤ 50 years old, but was not evident in patients > 50. In GB patients, no location-dependent survival benefit with GTR was observed.

The results demonstrate a complex interaction between tumor grade, frontal lobe location, and age in

their various contributions to the magnitude of survival benefit gained from GTR. The greatest survival benefit of GTR relative to STR was observed in patients age ≤ 50 with AAs in the frontal lobe [21].

Patients diagnosed with MGMT promoter unmethylated Glioblastoma from 2010 to 2012 who received radiation (RT) or chemoradiotherapy (CRT) were identified in the National Cancer Database. Logistic regression was performed to assess for predictors of receiving chemoradiation. The Kaplan-Meier method was used to assess overall survival (OS) by treatment group and Cox regression analysis was used to assess impact of covariates on OS.

There were 738 patients who met the study criteria, of which 107 (14.5%) received RT alone and 631 (85.5%) received CRT with median RT dose 6000cGy for both groups. Median follow up for living patients was 21.9 months. Ninety-two (12.5%) patients did not undergo any resection, 330 (44.7%) underwent a subtotal resection and 316 (42.8%) had a gross total resection. The median and 2-year OS was 16.8 months and 24.7% for RT alone compared to 15.6 months and 25.9% for the CRT group ($p = 0.250$). On multivariable analysis, the addition of chemotherapy had no impact on survival (HR 1.12, 95% CI 0.86-1.46, $p = 0.396$).

Despite the routine use of chemoradiation among patients with MGMT promoter unmethylated Glioblastoma, there does not appear to be a survival benefit compared to radiation alone [22].

Hansen et al., included prospectively recorded clinical data from 1364 adult patients with histologically verified glioblastoma from the Danish Neuro-Oncology Registry, 2009-2014.

The age standardized incidence rate was 6.3/100,000 person-years for males and 3.9 for females and the median age was 66 years. The median overall survival was 11.2 months. There was an independently significant prognostic effect of age, performance status, cognitive symptoms, tumor diameter, multifocality, crossing midline, and contrast enhancement. For partial and total resection compared to biopsy only, the adjusted risk of dying was reduced by 43% (HR [CI] 0.57 [0.48-0.68]) and 51% (0.49 [0.40-0.60]), respectively. For patients receiving a partial and full radiochemotherapy regimen compared to no postsurgical treatment, the risk reduction was 56% (HR [CI] 0.44 [0.37-0.53]) and 70% (0.30 [0.25-0.35]), respectively. The full radiochemotherapy regimen was only allocated to 50% of the patients, 29% among the oldest (70+ years) and 60% among the younger (18-69 years).

Glioblastoma patients had a poor overall survival but with several specific independent prognostic factors. Extensive cancer treatment was associated with an increasing survival in all age groups, but only half of the patients were sufficiently fit for a full regimen of postoperative combined radiochemotherapy [23].

2017

A study enrolled 60 glioblastoma patients with more than 5-mm-thick surgical cavity wall enhancement (SCWE)s as detected on contrast-enhanced MR imaging after concurrent chemoradiation therapy. Two independent readers categorized the shape and perfusion state of SCWEs as nodular or non-nodular and as having positive or negative perfusion compared with the contralateral grey matter on arterial spin labeling (ASL). The perfusion fraction on ASL within the

contrast-enhancing lesion was calculated. The independent predictability of TTP was analyzed using the Kaplan-Meier method and Cox proportional hazards modelling.

The perfusion fraction was higher in the non-progression group, significantly for reader 2 (P = 0.03) and borderline significantly for reader 1 (P = 0.08). A positive perfusion state and (P = 0.02) a higher perfusion fraction of the SCWE were found to become an independent predictor of longer TTP (P = 0.001 for reader 1 and P < 0.001 for reader 2). The contrast enhancement pattern did not become a TTP predictor.

Assessment of perfusion in early post-treatment MR imaging can stratify TTP in patients with glioblastoma for adjuvant temozolomide therapy. Positive perfusion in SCWEs can become a predictor of a longer TTP [24)].

2016

The Medicare database was searched to identify patients 66 years of age and older with glioblastoma, with and without infection, from 1997 to 2010. The primary outcome was survival after diagnosis. The statistical analysis was performed with a graphical representation using Kaplan-Meier curves, univariate analysis with the log-rank test, and multivariate analysis with proportional hazards modeling.

A total of 3784 patients with glioblastoma were identified from the database, and from these, 369 (9.8%) had postoperative infection within 1 month of surgery. In patients with glioblastoma who had an infection within 1 month of surgery, there was no significant difference in survival (median 5 months) compared with patients with no infection (median 6 months; p = 0.17). The study also showed that older age, increased Gagne comorbidity score, and having diabetes may be negatively associated with survival.

Infection after craniotomy within 1 month was not associated with a survival benefit in patients with glioblastoma [25)].

Álvarez de Eulate-Beramendi et al. retrospectively included all patients over 70 years of age, who underwent surgery at the Department of Neurosurgery (HUCA and HUMV) and were diagnosed of Glioblastoma by pathological criteria from January 2007 to September 2014. Results Eighty-one patients were analysed, whose mean age was 75 (SD 4) and 48 were male. Karnofsky performance status (KPS) was over 70 in 61 patients and 38.3% presented with motor deficit. Sixty-three patients underwent resection, and 18 had only a diagnostic biopsy. The complication rate was 17.28% and mortality rate was 7.4%. Survival was increased in patients who received radiotherapy (n = 41) or additional chemotherapy (n = 26) (p < 0.001). KPS < 70 was an independent factor associated with low-rate survival. Patients with optimal treatment had a median survival of 8 months compared to patients with suboptimal treatment who had a median survival of 4 months (p < 0.001). Conclusions This study suggests that KPS is the most important preoperative prognostic factor. Maximal safe resection followed by radical radiotherapy and temozolomide might be the optimal treatment of choice since glioblastoma-diagnosed patients over 70 years of age showed a statistically significant survival benefit [26)]

2015

With the publication of the European Organisation for Research and Treatment of Cancer/National Cancer Information Center EORTC NCIC protocol, concomitant radiochemotherapy followed by intermittent chemotherapy became the new treatment standard for patients with primary glioblastoma.

Eight years after widespread introduction of this protocol, it is of interest to investigate whether this new standard has been established in daily neuro-oncologic practice.

Rapp et al. analyzed primary glioblastoma patients diagnosed between 2005 and 2013 treated at the Heinrich Heine Medical Centre, Düsseldorf, Germany according to the EORTC/NCIC trial. Parameters associated with treatment performance (interruption of radiotherapy, concomitant chemotherapy and intermittent chemotherapy, total number of cycles, and side effects) were retrospectively analyzed and compared with the available data from the EORTC/NCIC trial.

In this single-center retrospective study, they identified 189 patients (116 men, 73 women; median age: 62 years) who were treated according to the EORTC/NCIC trial protocol.

A total of 176 patients received cytoreductive surgery; 13 patients had stereotactic biopsy only (EORTC/NCIC trial: 239 patients and 48 patients, respectively). Radiotherapy had to be interrupted in 9 patients (5%) (EORTC/NCIC trial: 15 patients [5%]) and concomitant chemotherapy in 26 patients (14%) (EORTC/NCIC trial: 37 patients [13%]). In 156 patients (83%), adjuvant TMZ chemotherapy was initiated (6 median temozolomide [TMZ] cycles; range: 1-30). In the EORTC/NCIC trial, 223 patients (47%) received the intermittent chemotherapy protocol (median: 3 cycles; range: 1-7). Overall, 97 patients (62%) completed 6 TMZ cycles (EORTC/NCIC-trial: 105 patients [47%]); dose escalation to 200 mg/qm at the second cycle was performed in 91 patients (58%) (versus 149 patients [67%]). Intermittent TMZ therapy was discontinued in 59 patients (38%) (versus 118 patients [53%]). Median overall survival in our patient cohort was 19 months (versus 14.6 months); median time to progression was 9 months (versus 6.9 months).

Comparison between the feasibility of the treatment protocol established by the EORTC/NCIC trial (performed within the setting of a prospective randomized trial) and the daily routine in a dedicated neurosurgical neuro-oncologic department demonstrates that the protocol is suitable for daily practice within a neurosurgical unit [27)].

A total of 126 patients were reviewed. Median progression-free survival was 5 months (95% confidence interval [CI], 4.138 to 5.862 months). Median overall survival (OS) was 8 months (95% CI, 5.950 to 10.050 months). Univariate analysis showed the statistically significant associations between the higher OS and age <70 (P = 0.046), Karnofsky performance status ≥70 (P = 0.001), single lesions (P = 0.007), lesions affecting one lobe (P = 0.007), total resection (P = 0.048), and Charlson Comorbidity index ≤5. Multivariate analysis identified the completion of 60 Gy radiotherapy and completion of 6 or more cycles of temozolomide chemotherapy as independent prognostic factors positively correlated with increased survival.

Maximal resection and radiochemotherapy treatment completion are associated with longer OS, and age alone should not preclude elderly patients from receiving surgery and adjuvant treatment. However, only a few patients were able to finish the proposed treatments. Poor performance and high comorbidity index status might compromise the benefit of treatment aggressiveness and must be

considered in therapeutic decision [28].

2013

Of 345 patients, 273 underwent open tumor resection and 72 biopsies; 125 patients had gross total resections (GTRs) and 148, incomplete resections. Surgery-related morbidity was lower after biopsy (1.4% versus 12.1%, P = 0.007). 64.3% of patients received radiotherapy and chemotherapy (RT plus CT), 20.0% RT alone, 4.3% CT alone, and 11.3% best supportive care as an initial treatment. Patients ≤60 years with a Karnofsky performance score (KPS) of ≥90 were more likely to receive RT plus CT (P < 0.01). Median overall survival (OS) (progression free survival; PFS) ranged from 33.2 months (15 months) for patients with MGMT-methylated tumors after GTR and RT plus CT to 3.0 months (2.4 months) for biopsied patients receiving supportive care only. Favorable prognostic factors in multivariate analyses for OS were age ≤60 years [hazard ratio (HR) = 0.52; P < 0.001], preoperative KPS of ≥80 (HR = 0.55; P < 0.001), GTR (HR = 0.60; P = 0.003), MGMT promoter methylation (HR = 0.44; P < 0.001), and RT plus CT (HR = 0.18, P < 0.001); patients undergoing incomplete resection did not better than those receiving biopsy only (HR = 0.85; P = 0.31).

The value of incomplete resection remains questionable. If GTR cannot be safely achieved, biopsy only might be used as an alternative surgical strategy [29].

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