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BACKGROUND: Patients with glioblastoma (GBM) have a poor prognosis following an extensive resection, radiotherapy (RT) and concomitant/adjuvant temozolomide (TMZ). Once GBM progresses after SOC, lomustine is the standard second-line treatment, while rechallenge with TMZ may be employed in selected patients with methylated promoter of MGMT, and bevacizumab is reserved for patients with extensive edema and need for steroids. New treatment modalities have been investigated at first recurrence, including alternating electric fields (TTFields) or antibody direct against epidermal growth factor receptor (EGFR), such as depatuximab mafodontin (ABT-414, Depatux-M), that have shown some activity in terms of disease control and progression-free survival (PFS). CLINICAL PRESENTATION: In September 2018, a 38 year-old man developed reduced strength in left upper limb and daily focal seizures. MRI showed an enhancing right fronto-temporal lesion which was subtotally removed with a diagnosis of glioblastoma (IDH 1/2 wild type, MGMT methylated - 40%, EGFR amplified, EGFRvIII positive). As the patient had a poor KPS (50), in October 2018 a hypofractionated RT (DFT 40 Gy/15 fractions) with concomitant TMZ (140 mg/day) was performed, followed by adjuvant standard TMZ (340 mg/day); however, chemotherapy was stopped after 3 cycles due to local progression on MRI coupled with strength worsening, increased seizure frequency, and need for steroids. Pseudoprogression was ruled out due to tumor growth out of the field of RT. Based on the high level of methylation of the MGMT promoter and EGFR amplification, a combined treatment with metronomic TMZ (100 mg/day continuously) plus Depatux-M (1.25 mg/kg every 2 weeks) was started (February 2019), but a brain MRI performed after 3 months of treatment displayed no significant changes on both MRI and neurological status. At this time point (May 2019) TTFields treatment was added. An initial decrease of tumor size was observed on MRI after 5 months, while a reduction of tumor size more than 90% has been progressively achieved after 1 year of treatment (April 2020). Moreover, a seizure-free status was observed without changing the antiepileptic medication. The patient developed a grade 3 ocular side effect (CTCAE version 5.0) with photophobia, blurred vision, foreign body sensation in the eyes after 6 months of treatment, which improved after dose delays and dose reduction of Depatux-M. The patient is still alive, and free of progression after 30 months and 25 months from diagnosis and first recurrence, respectively. CONCLUSION: To our knowledge, this is the first report of a recurrent GBM with a significant and long-lasting neuroradiological response following a combined treatment with TTFields, Depatux-M, and intensified schedule of TMZ. A synergistic effect of TTFields with compounds interfering with the microtubular system should be further investigated.

P14.78 COMPARISON OF PROGRESSION-FREE SURVIVAL AFTER REIRRADIATION OF LOCAL AND DISTANT GLIOBLASTOMA'S RELAPSES

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BACKGROUND: Despite using of modern comprehensive approaches to the treatment of patients with glioblastomas (GB) it invariably recur after a median interval of less than 7 months. Relapses are inevitable and is often the leading cause of death in patients. About 80–90% of recurrences are local, distant relapses are 5–20%. The optimal treatment strategy of recurrent GB have not yet been determined. MATERIAL AND METHODS: The analysis included 130 patients with 160 lesions after primary combined treatment. Progression was assessed based on the RANO criteria. All patients have been re-irradiated in various regimens: 26 pts with median dose 60 Gy/30 fr, 20 pts with median dose 45 Gy/15 fr, 74 pts with dose 24-35Gy for 3–7 fr., 10 pts with median dose 22Gy/1fr. The scheme and regimen of fractionation were determined by tumor volume, localization and functional status of patient. Chemotherapy was changed to a regimen with Bevacizumab (BVZ) before the re-irradiation. According to the EORTC criteria lesions were divided as local (n=112) and distant (n=48) progression with median volume 23.6 cc and 14.7 cc respectively. RESULTS: The median progression-free survival in the whole group was 8.2 months(95% CI 7–8.7). Progression-free survival at 6; 12 and 24 months was 65.8%; 21.9% and 4% respectively. Progression-free median survival after treatment of local and distant glioblastoma recurrences was different: 7.6 and 9.2 months, respectively (p = 0.048). In 17.4% radiation necrosis was detected according to MRI and 11C-methionine PET-CT data. Steroid and BVZ therapy were effective in these cases, no one of them was reoperated. CONCLUSION: Re-irradiation for GB recurrences is effective and safe way for improvement of outcomes in patients with progression. In the group of patients with local relapses, local control is lower than in the group of distant ones. It may associated with the increasing of the radioresistance of tumor cells after the initial combined treatment. Further studies are needed to compare and assess the role of radiobiological and others factors in the development of local and distant recurrence.The research was supported financially by RFBR (Project No. 18-29-01061).

P14.79 DIFFERENTIATION OF TREATMENT-RELATED CHANGES FROM TUMOR PROGRESSION FOLLOWING BRACHYTHERAPY IN PATIENTS WITH WHO II AND III GLIOMAS USING FET PET

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BACKGROUND: Following brachytherapy, the differentiation of radiation-induced changes (e.g., radiation necrosis) from actual tumor progression using MRI is challenging. To overcome this diagnostic uncertainty, we evaluated the diagnostic value of O-(2-[^{18}F]-fluoroethyl)-L-tyrosine (FET) PET in glioma patients treated with brachytherapy. MATERIAL AND METHODS: From 2006–2019, we retrospectively identified WHO grade II or III glioma patients (i) treated with brachytherapy using Iodine-125 seeds, (ii) equivocal or progressive MRI findings inside the radiation field, and (iii) additional FET PET imaging for diagnostic evaluation. Static FET PET parameters such as maximum and mean tumor-to-brain ratios (TBR) and dynamic FET PET parameters (i.e., time-to-peak, slope) were obtained. Diagnostic performances were calculated using receiver operating characteristic curve analyses and Fisher's exact test. Diagnoses were confirmed histologically or clinicoradiologically. RESULTS: Following brachytherapy, suspect MRI findings occurred after a median time of 33 months (range, 5–111 months). In 10 of 21 patients (WHO grade II, n=5; WHO grade III, n=16), treatment-related changes were diagnosed. The best diagnostic performance for identification of treatment-related changes was obtained using maximum TBRs (threshold <3.20; accuracy, 86%; sensitivity, 100%; specificity, 73%; P=0.007). Mean TBRs reached an accuracy of 76% (threshold <2.05; sensitivity, 89%; specificity, 64%; *P*=0.010). Dynamic PET parameters did not reach statistically significant results. CONCLUSION: Our data suggest that static FET PET parameters add valuable diagnostic information to diagnose radiation-induced changes in glioma patients treated with brachytherapy.

P14.81 BRAIN METASTASES OF LUNG ADENOCARCINOMA - CLINICOPATHOLOGICAL PROFILE AND OUTCOMES OF A SINGLE-CENTRE

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BACKGROUND: Brain metastases (BM) in patients with non-small cell lung cancer (NSCLC) are considered a major determinant of overall survival (OS). Historically, surgical resection (SR), stereotactic radiosurgery (SRS), or/and whole-brain radiation therapy (WBRT) followed by chemotherapy has been the treatment modalities for BM from lung adenocarcinoma. Recent insights into the biology of adenocarcinoma have led to a wealth of novel therapies, including tyrosine kinase inhibitors (TKIs). Here, we review the pattern of brain metastasis in lung adenocarcinoma patients and management strategies in our centre. MATERIAL AND METHODS: We performed a single-centre retrospective analysis of patients with lung adenocarcinoma and BM between 2017–2020. Data were collected from electronic medical records, including clinical and histopathological features and outcomes. Survival curves were estimated with the Kaplan-Meier method and compared using the log-rank test. RESULTS: We identified 29 patients, 65% male, median age 65 years (range 38–84); 55% ECOG PS 0–1; 59% smokers; 55% had extracranial metastases (ECM) and 66% were symptomatic, 24% were EGFR mutated, the frequency of ALK rearrangement was 14%, in 14% the molecular testing was not performed. We treated 59% with WBRT, 12% with SRS, 11% with SR+WBRT and 4% with SR+SRS; 14% were referred for palliative care. Clinical deterioration during local therapy was observed in 32% of the patients and, consequently, they haven't undergone systemic treatment. After local treatment, 26% received chemotherapy (CT) and 28% received TKIs therapy. Median OS (mOS) was 11.3 months (95% CI 2.4–20.3) for the CT subgroup; mOS for the TKIs subgroup was not reached, but the 1-year survival rate was 67%. CONCLUSION: BM confers a worse prognosis in lung adenocarcinoma patients. Currently, targeted systemic treatments in patients with driver mutations improve survival and have demonstrated efficacy in lung adenocarcinoma metastatic to the

brain. Further research is needed to find better treatments for BM in NSCLC patients with no driver mutations.

P14.82 GLIONEURONAL TUMORS - A RARE TUMOR ENTITY WITH DIAGNOSTIC AND THERAPEUTIC CHALLENGES: REPORT OF TWO CASES AND REVIEW OF LITERATURE

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BACKGROUND: The 2007 WHO classification of brain tumors first encompassed two new entities of glioneuronal tumors, including papillary glioneuronal tumors (PGNT) and rosette-forming glioneuronal tumours. The reviewed version of the 2016 WHO classification additionally included diffuse leptomeningeal glioneuronal tumours. The histopathological, genetic, and clinical understanding of glioneuronal tumors is currently evolving, however there are no guidelines for diagnostic and clinical management yet. MATERIAL AND METHODS: We report two male patients with glioneuronal tumors and performed a review of literature. RESULTS: The first patient was diagnosed with a PGNT (MIB-1 proliferation index = 5%) located in the right parietal lobe at the age of 33 years and received surgical resection. Two years later, the tumor recurred in the same location. A second tumor resection was performed followed by concomitant radiochemotherapy with temozolomide (60/2 Gray). A next-generation sequencing gene panel (Oncomine) confirmed the initial diagnosis of a PGNT. The patient has remained in remission for the past 10 years. The second patient developed complex partial seizures which were first misdiagnosed as anxiety disorder at the age of 26 years. An MRI scan revealed a contrast-enhancing bifrontal cystic lesions 5 years later and he received a gross total tumor resection. The diagnosis of a glioneuronal tumor was made, however molecular pathology and methylation analysis were not able to classify the tumor entity further. There was no evidence of tumor recurrence one year after surgery and he remained seizure-free with antiepileptic treatment. CONCLUSION: Glioneuronal tumors encompass rare and heterogenous tumor entities which primarily present in young patients and often show a favorable clinical course. Although the increasing number of reports in the literature have improved our understanding of these tumors, uncertainty remains in diagnostic challenging cases and patients with progressive disease after surgery. The value of next-generation sequencing and the choice of adjuvant treatment modalities have not been systematically evaluated in this patient group.

P14.85 IMPACT OF THE NEURO-RADIOLOGIST AND NEURO-SURGEON IN CONTOURING WITH THE NEURO-ONCOLOGIST ON LOCAL RELAPSE RATES FOR BRAIN METASTASES TREATED WITH STEREOTACTIC RADIOSURGERY

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BACKGROUND: The audit evaluates the value of MDT, including neuro-radiologist and neuro-surgeon, review of contouring carried out by a clinical oncologist in stereotactic radiosurgery (SRS). MATERIAL AND METHODS: A sequential audit was conducted of all patients receiving intracranial SRS at our local institution for the first 22 months of a new SRS service. Lesions were contoured first by clinical oncologist then reviewed/edited by the MDT. The initial contour was compared with final contour using Jaccard conformity and geographical miss indices. The dosimetric impact of a contouring change was assessed using plan metrics to both original and final contour. The impact of the contouring review on local relapse, overall survival and radio necrosis rate was evaluated with at least 24 months follow up (24–46 months). RESULTS: 113 patients and 142 lesions treated over 22 months were identified. Mean JCI was 0.92 (0.32–1.00) and 38% needed significant editing (JCI<0.95). Mean GMI was 0.03 (0.0–0.65) and 17% showed significant miss (GMI>0.05). Resection cavities showed more changes, with lower JCI and higher GMI (p<0.05). There was no significant improvement on JCI or GMI shown over time. Dosimetric analysis indicated a strong association of conformity metrics with PTV dose metrics; a 0.1 change in GTV conformity metric association with 6–17% change in dose to 95% of resulting PTV. Greater association was seen in resection cavity suggesting the geographical nature of a typical contouring error gives rise to greater potential change in dose. Clinical outcomes compared well with published series. Median survival was 20 months and local relapse free rate in the treated areas of 0.89 (0.8–0.94) at 40 months, and 0.9 (0.83–0.95) radio-necrosis free rate at 40 months with a median 17 months to developing radio-necrosis for those that did. CONCLUSION: This work highlights that a MDT contour review adds significant value to SRS and the approach translates into reduced local recurrence rates at our local institution compared with previously published data. Radio-necrosis rates are below 10%. No improvement in clinical oncologist contouring over time was shown indicating a collaborative approach is needed regardless of experience of clinical oncologist. MDT input is recommended in particular in contouring of resection cavities.

P14.86 PREDICTIVE VALUE OF MGMT PROMOTER (PMGMT) METHYLATION STATUS ON PSEUDOPROGRESSION (PSP) AND SURVIVAL ANALYSIS IN GLIOBLASTOMA (GBM) PATIENTS: A RETROSPECTIVE SINGLE INSTITUTIONAL ANALYSIS

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BACKGROUND: Glioblastoma is the most common and aggressive primary brain tumor. Conventional therapies, such as maximal extension of surgery followed by radiotherapy (RT) and chemotherapy with Temozolomide (TMZ) have not resulted in major improvements in terms of patients' outcome, overall survival (OS) still remaining poor. In this context, radiological response assessment after radiotherapy remains challenging due to the potential effect of radionecrosis, often mimicking tumor progression. Differentiation between PsP and true progression is required to avoid further unnecessary surgeries, or the premature discontinuation of TMZ. It is known that pMGMT methylated patients respond better to chemotherapy than unmethylated counterpart, so, tumor cells necrosis can be enhanced in this setting. The aim of the study is to observe the correlation between pMGMT methylation status with the incidence of PsP in GBM patients at the first radiological evaluation after RT. MATERIALS AND METHODS: Patients with histologically diagnosis of GBM from 2017 to 2021 and availability of pMGMT methylation status were enrolled. PsP was radiologically defined at first brain MRI after RT in case of increasing size of the enhancing component and of peritumoral oedema that remain stable or decrease after antioedema therapy, such as a clinical improvement was observed. RESULTS: We analysed 55 GBM patients, 35 (64%) displayed pMGMT methylation whereas 20 (36%) resulted pMGMT unmethylated. PsP was evident in 29 patients (53%), all of them showed methylation of pMGMT. In our analysis, none of pMGMT unmethylated patients experienced PsP. Regarding survival outcome for pMGMT methylated patients, our analysis shows a mPFS of 8.7 (95% CI: 5–10) months versus 9.3 (95%CI: 4.6–12.3) months in methylated and unmethylated respectively (p=0.87). CONCLUSIONS: Methylation status of pMGMT showed to be predictor of PsP in GBM patients. If validated, this information could be very useful to guide clinicians in differentiating PsP from true progression. To date, our survival analysis regarding PFS showed no statistical difference among methylated patients with respect to the presence or absence of PsP. Thus, PsP seems not to be a marker of responsiveness to common treatment. Further data are needed to validate our results.

P14.87 SIGNIFICANCE OF CLINICAL AND MOLECULAR-GENETIC FACTORS FOR PROGNOSIS IN 574 ADULT PATIENTS WITH PRIMARY GLIOBLASTOMA

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BACKGROUND: Despite advances in the characterization of genomic alterations in glioblastoma patient survival remains poor. The aim of this single center retrospective study was to estimate prognostic factors affecting to survival for optimizing personalized treatment strategy in glioblastoma patients. MATERIAL AND METHODS: 574 consecutive patients with primary glioblastoma treated at the Burdenko National Medical Research Center of Neurosurgery from 2014 to 2019 were included in this study (314 male /260 female). Survival data was analyzed using Kaplan-Meier with log-rank tests to assess statistical significance. A linear regression model was built to predict overall survival. RESULTS: Older patients (> 45 years) had the worse prognosis than patients ≤ 45 (p = 2.37 * 10^-6). Female patients had advantages in overall survival (p = 0.014). Time interval from surgery to the starting of radiotherapy longer than 4 weeks was associated with worse overall survival (p = 0.062). Patients with positive IDH1/2 and MGMT had better prognosis than patients with wild type and MGMT negative (p = 0.000841, p = 0.000138, respectively). We revealed that there were significant differences in overall survival between patients who had progression on the first (p = 0.000312), second (p = 0.001046) and third (p = 0.00223) follow-up MRI after radiotherapy. Median survival times (from the date of surgery) were 17, 20, 23 months, respectively. The feature importance in the linear regression model was patient's age, IDH1/2 mutation, MGMT promoter methylation status, progression on the first follow-up MRI and sex. CONCLUSION: Older patient's age, prolonged time between surgery and RT starting, male sex, negative IDH1/2 and MGMT, progression on the first MRI were associated with poor overall survival in glioblastoma patients. Our results suggested additional clinical, radiomics and molecular-genetic data should be added to improve the overall survival prediction.

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