ation, we further investigated nuclear localisation of beta-catenin levels. The results showed the both beta-catenin and c-myc expression in the nucleus was suppressed after combination therapy. CONCLUSION: In meningioma cells, radiotherapy in combination with HDAC6 inhibitor reduces the nuclear localisation of beta-catenin and synergistically decreases cell survival. Our findings demonstrate a potential therapeutic strategy of Cay10603 to improve the radiosensitisation for meningioma cells.

P18.05.A. BEVACIZUMAB IN ATYPICAL AND ANAPLASTIC MENINGIOMAS: THE BEMEN STUDY

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BACKGROUND: meningiomas are the most frequent primary brain tumours. The current standard treatment for atypical and anaplastic meningioma can include surgical resection and radiotherapy. Despite the high rate of relapse no systemic treatment is indicated. Few data are available regarding the effectiveness of bevacizumab (BEV) in this setting. We performed a retrospective analysis investigating the efficacy and safety of BEV in meningioma patients relapsed after receiving surgery and radiotherapy. Gene mutations were also collected MATERIAL AND METHODS: we retrospectively analyzed patients treated with off-label BEV at the Veneto Institute of Oncology from July 2019 to February 2022. Major inclusion criteria were histologically-confirmed diagnosis of grade 2-3 meningioma (according to WHO 2016 classification), previous treatment with surgery and radiotherapy, no indication to further surgical reintervention or reirradiation, absence of major contraindications to the use of BEV. Data were estrapolated from local clinical records. Bevacizumab was administered at 10 or 5mg/Kg every 2 weeks (at physician's discretion) until progressive disease/death or unacceptable toxicity. Kaplan-Meier curves were used to estimate the survival rate; CTCAE v 5.0 was used to estimate treatment-related toxicities; RANO criteria were used for radiological assessment; NGS Foundation One panel was used to examine molecular data RESULTS: the median follow up was 13 months (3-30 range). 26 patients were enrolled. Median age was 68 ys (29-84); male pts were 16 (61%); 61% (16 pts) with atypical meningioma, 38.5% (10 pts) with anaplastic meningioma; 27% (7 pts) had underwent 2 or more surgeries; 58% had had 2 or more RT treatments; 96.1% (25 pts) received <2 previous lines of systemic treatment. 77% (20 pts) and 23% (6) received BEV 10 and 5mg/Kg every 2 weeks, respectively. For 61% of patients (16 pts), NGS analyses were available; 62% (10 pts) harboured NF2 mutations (1 patient had a confirmed diagnosis of neurofibromatosis type 2), 23% (6 pts) CDKN2A/2B deletion, 11% (3 pts) PTEN mutation, 8% (2 pts) FGFR mutation, 8% (2 pts) JAK alteration. Overall survival (OS) rate was 82% and 62% at 6 and 12 months respectively; 6 months PFS rate was 83%. 4 patients showed PR, 11 SD, 6 PD, no patient had CR; 5 patients were not evaluable for response. Among evaluable patients the disease control rate (stability+response) was 71% and the objective response rate was 19%. Median PFS and OS were not reached19% (5 pts) experienced CTCAE grade 1 or 2 toxicity, mainly hypertension (4 pts); 1 patient experienced grade 3 hypertension. CONCLUSION: BEV showed very promising activity in recurrent grade 2-3 meningioma. The treatment was well tolerated. BEV should be considered an optimal therapeutic option in this setting of meningioma patients. The NGS results might be useful in identifying targetable mutations in case of further recurrence

P18.06.B. ETS-TRANSCRIPTION FACTOR INHIBITORS ARE EFFECTIVE IN *TERT* PROMOTER MUTATED MENINGIOMA CELLS IN VITRO

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BACKGROUND: *TERT* promoter mutations in meningiomas were recently found to be strongly prognostic and associated with malignant progression and risk of recurrence. As result, the mutation in the *TERT* promoter generates a binding site for E twenty-six (ETS) transcription factors. Consequently, ETS-transcription factor inhibition might represent a novel strategy to impede meningioma growth. In a prior study we could demonstrate effectiveness of the ETS-transcription factor inhibitor YK-4-279 in TERT promoter mutant meningiomas. Recently, TK216 the clinical derivative of YK-4-279 was developed. Therefore, we aimed to clarify whether TK216 might have an increased effect as compared to YK-4-279 in TERT promoter mutated meningioma cells in vitro. METHODS: A meningioma-derived cell line (BTL695) generated from a TERT promoter mutated (C228T) anaplastic meningioma served as cell model for the experiments. BTL695 was characterized by high telomerase activity and TERT mRNA expression as analysed by the TRAP assay and RT-PCR, respectively. Genomic aberrations were verified using Ion Torrent Oncomine Comprehensive Assay v3-based next-generation sequencing (NGS). The sensitivity of BTL695 to YK-4-279 and TK216 was determined using an MTT-based viability assay (EZ4U). To elucidate the effectiveness of TK216 on cell cycle and apoptosis, cells were stained with PI and annexin V, respectively, and measured by flow cytometry. The effect of TK216 on the protein expression of the cleaved poly(ADP-ribose) polymerase-1 (PARP-1), indicative for apoptosis, was investigated by western blot. Additionally, a TK216-resistant cell model (BTL695res) was generated and analysed by NGS. RESULTS: BTL695 was significantly more sensitive to TK216 as compared to YK-4-279 ($p<0.0001$) characterized by the distinctly lower IC50 value of TK216 exposed cells (0.7 µM TK216; 1.6 µM YK-4-279). Flow cytometry analysis revealed a TK216 induced G2M cell cycle arrest and increased apoptosis rate, which was additionally verified by the expression of cleaved PARP-1 expression using western blot. Genomic aberrations were found in 18 genes including NF2, CDKN2A/B, ARID1A and PTEN. Interestingly, although the majority of genomic alterations was persistent in the TK216 resistant cell model, a p53 mutation was newly acquired as compared to the parental cell line. CONCLUSION: In summary, our results indicate that ETS transcription factor inhibition by TK216 exerts antitumour activity in our TERT promoter mutant meningioma cell model. Additionally, the sensitivity against TK216 is superior to YK-4-279 and therefore TK216 may represent a promising new therapeutic option for patients with aggressive, *TERT* promoter mutated meningioma.

P18.07.A. HIPPO SIGNALING PATHWAY IS STRONGLY INVOLVED IN MENINGIOMA TUMORIGENESIS

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BACKGROUND: Recurrent and aggressive meningiomas remain an unmet medical need in neuro-oncology. In mammals, Hippo signaling pathway is responsible for the growth of organs by regulating cell proliferation and apoptosis. The tumor suppressor NF2 protein belongs to the core of the Hippo pathway and a defect of its gene is present in 50% of meningiomas. Absence of NF2 keeps Hippo pathway inactive allowing the translocation of YAP/TAZ to the nucleus and the formation of a complex with TEADs. This complex then promotes the transcription of anti-apoptotic and proliferative genes such as *CTGF*, *CYR61* and *AXL*. Here we present experimental results on human meningioma fragments and primary cell cultures supporting that Hippo pathway plays a critical role in meningioma tumorigenesis. MATERIAL AND METHODS: The role of the Hippo pathway was studied on 57 meningiomas, well characterized at clinical, histological and molecular level. The genomic profile, target transcripts of the complex YAP/TAZ-TEADs, cell viability, and cell proliferation were analyzed after siRNA transfection targeting YAP, TAZ, YAP+TAZ and TEADs. RESULTS: Fifty-seven meningiomas were randomly selected including 27 WHO grade II and III tumors. Thirty (53%) presented a defect on the *NF2* gene (*NF2*def) including 19(65%) grade II/III. *NF2*def meningiomas presented a significant increase of expression levels of Hippo pathway target transcripts CTGF, CYR61 and AXL in comparison with *NF2* wild-type tumors ($p<0.0001$, $p=0.0072$ and $p=0.0191$, respectively). This increase was not correlated with the grade, the sex or with the cerebral localization of the meningiomas. On the other side, IHC analysis suggested this increase was correlated with the nuclear localization of YAP. Disturbing the YAP/TAZ-TEADs complex using siRNA on 10 meningiomas (5 *NF2* wild-type and 5 *NF2* def) induced a significant decrease on cell proliferation but not on cell viability. This decrease was more important when TAZ was turned off in comparison to turning off of YAP. CONCLUSION: Our experimental results strongly support the importance of the Hippo pathway in meningioma tumorigenesis, supporting its relevance as a new target in meningioma therapy. A.Barlier reports receiving research grants from Inventiva Pharma. No potential conflicts of interest were disclosed by the other authors.

P18.08.B. FULLY AUTOMATIC MENINGIOMA SEGMENTATION USING T1-WEIGHTED CONTRAST-ENHANCED MR IMAGES ONLY

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BACKGROUND: Manual segmentation of brain tumors requires expertise, is time-consuming, and is subject to inter-rater variability. Fully automatic brain tumor segmentation is possible for glioma and meningioma when

volumetric T1, T1 contrast-enhanced (T1c), T2, and Fluid-attenuated inversion recovery (FLAIR) MRIs are available. In clinical care of meningiomas, however, often only volumetric T1c scans are available. In this work, we trained a deep learning network to segment meningiomas using only T1c scans for use in clinical research. MATERIAL AND METHODS: NnU-Net, a deep learning model that is optimized for medical image segmentation, was trained to segment meningiomas from T1c images. This was performed on a large clinically collected meningioma dataset (n=374) of T1c scans with semi-automatically generated enhancing tumor masks and additional data from the BraTS2020 glioma dataset. Model performance was compared against inter-rater reliability, between different models, between anatomical tumor locations, and against models using multiple MRI modalities. RESULTS: The best performing model obtained a Dice score of 0.90. This performance was 0.03 points lower when compared to inter-rater reliability (Dice=0.93) and almost equal to models using multiple MRI modalities. Model performance split over anatomical tumor locations was between 0.90 and 0.97 (Dice). CONCLUSION: Fully automatic meningioma segmentation using only T1c images is possible with an accuracy that is similar to inter-rater reliability and models using multiple imaging modalities.

P18.09.A. SINGLE-SESSION STEREOTACTIC RADIOSURGERY FOR LARGE PARASELLAR MENINGIOMAS

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BACKGROUND: The purpose of this study is to assess the long-term efficacy and safety of single-session stereotactic radiosurgery for large (10 cc or more) perioptic intracranial benign meningiomas. MATERIAL AND METHODS: In this retrospective study we included 175 patients with large perioptic benign meningiomas (≥ 10 cc) who were treated by single-session SRS. Perioptic meningiomas were defined as meningiomas touching, compressing or within 3 mm of the optic pathway. The median tumor volume was 15 (10-57.3 cc (IQR 8.4 cc)). The median prescription dose was 12 Gy (9-14 Gy (IQR 1 Gy)). RESULTS: The median follow up period was 72 months (13-217 months (IQR 65 months)). The tumor control rate was 92%. The PFS at 5- and 10- years was 97% and 80%. Favorable (better/stable) visual outcome was reported in 169 patients (97%) and unfavorable (worse) outcome in 6 patients (3%). Temporary adverse radiation effects were observed in 21 patients (12%) but only 7 (4%) were symptomatic. Sixty-three patients had a blind/non-useful eye according the pre-treatment visual field examination. Visual improvement was observed in blind/non-useful eye in 17 patients (27%) while vision remained unchanged in 46 patients (73%). Ocular nerve palsy improved in 36 patients (61%). Tumor shrinkage was not a prerequisite for cranial nerve improvement. CONCLUSION: Stereotactic radiosurgery provides an effective and safe treatment option for large perioptic meningiomas.

P18.10.B. NATURAL HISTORY OF MENINGIOMAS - A SERIAL VOLUMETRIC ANALYSIS OF 240 TUMORS

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BACKGROUND: The management of asymptomatic intracranial meningiomas is controversial. Through the assessment of growth predictors, we aimed to create the basis for practicable clinical pathways for the management of these tumors. MATERIAL AND METHODS: We volumetrically analyzed meningiomas radiologically diagnosed at our institution between 2003 and 2015. For this purpose, we used exclusively thin-layered MR images (i.e. ≤ 2mm slice thickness). The primary endpoint was tumor growth defined as a 14.35% increase in tumor volume. We identified predictive clinical and radiological characteristics and used the significant variables from a multivariable regression model to construct a decision tree based on the exhaustive Chi-squared Automatic Interaction Detection (exhaustive CHAID) algorithm. RESULTS: Of 240 meningiomas, 159 (66.3%) demonstrated growth during a mean observation period of 46.9 months. On multivariable logistic regression analysis, older age (OR=0.979 (0.958-1.000), p=0.048) and presence of calcification (OR=0.442 (0.224-0.872), p=0.019) had a negative predictive value for tumor growth, while T2-signal iso-/hyperintensity (OR=4.415 (2.056-9.479), p<0.001) had a positive predictive value. A decision tree model yielded three growth risk groups based on T2-signal intensity and presence of calcifications with a proportion of growing tumors of 34.1% in the low risk group, 60.0% in the intermediate risk group and 80.2% in the high risk group. Median tumor volume doubling time (Td) was 185.7 months in the low risk, 100.1 months in the intermediate risk and 51.7 months in the high risk group (p<0.001). While 0% of meningiomas in the low and intermediate risk group had a Td of ≤12 months, 8.9% in the high risk group did so (p=0.021). CONCLUSION: Most meningiomas demonstrated growth during follow-up. The presence or absence of calcifications and the signal intensity on T2-weighted imaging allow a practical and simple stratification of meningiomas into low, intermediate and high risk tumors. Small tumors in the low or intermediate risk categories can be monitored with longer follow-up intervals, whereas in the high risk category proactive management decisions can be justified.

P18.11.A. ACTIVE BEAM SCANNING PROTON THERAPY FOR LARGE SKULL BASE BENIGN MENINGIOMAS: LONG-TERM RESULTS

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PURPOSE: To report long-term results of active beam scanning proton therapy (PT) for large skull base benign meningiomas MATERIAL AND METHODS: Eighty-two patients (pts) with large skull base meningiomas were treated with PT between April 2015 and December 2021. Median age was 62 years (range, 48-82) while KPS ranged between 60 and 100 (median 90); 60 were female (73%), and 22 were male (27%). Thirty-two pts (39%) had histologically proven World Health Organization (WHO) Grade I tumors. In remaining pts diagnosis was based on the typical imaging appearance of benign meningioma. All patients received PT for residual, progressive or non-operable lesions. Newly diagnosed tumors received total dose of 50 GyRBE (RBE: relative biologic effectiveness) while progressing meningiomas 54 GyRBE. All the treatments were delivered at 2 GyRBE per fraction. All pts were treated with active beam scanning PT using 3 fields with single field optimization technique. Treatment planning was based on morphological magnetic resonance imaging (MRI) with contrast enhancement medium administration. All pts received also 68-Ga-DOTATOC-PET. Gross tumor volume ranged from 21 to 64 cc. Toxicity was assessed according to Common Terminology Criteria for Adverse Events version 4.0. Median follow-up time was 40 months (range, 3-83). RESULTS: All pts completed the treatment without breaks. Registered acute side effects include grade 1 (19%) and grade 2 (8%) skin erythema, grade 1 (5%) and grade 2 (5%) alopecia, grade 1 (40%) fatigue, grade 1 (5%) and grade 2 (10%) conjunctivitis, grade 1 (10%) pain, grade 1 (5%) blurred vision, grade 1 (10%) headache, and grade 2 (5%) skin hyperpigmentation. One pts (1%) experienced grade 3 pain. There were no further grade 3 or higher acute toxicities. Registered late side effects include grade 1 (2%) and grade 2 (5%) alopecia, grade 1 (21%) fatigue, grade 1 (5%) and grade 2 (5%) headache, grade 1 (6%) dizziness, grade 1 (3%) blurred vision, grade 1 (3%) and grade 2 (6%) pain, grade 1 (2%) dry eye, and grade 1 (5%) skin hyperpigmentation. Two pts (2%) experienced grade 3 pain. Two further pts (2%) experienced grade 3 optic neuropathy. There were no further grade 3 or higher late toxicities. During follow-up one pts (1%) with cavernous sinus meningioma experienced complete obstruction of intracavernous carotid artery with mild transient symptoms that resolved in few days and brain tissue ischemia detected at MRI (grade 2). Before irradiation this pts already had a meningioma-related near-complete obstruction of the intracavernous carotid artery and received a vascular surgery evaluation. Currently, absolute tumor control is 99%. Moreover, relief of symptoms recorded before irradiation occurred in 40% of pts. CONCLUSION: PT is safe and effective treatment for pts with large skull base benign meningiomas.