P12.06 Significantly Mutated Genes for Radiation-Associated Meningioma

and bone when infiltrated. The histological grading is the most important prognostic factor. Meningiomas may recur after total surgical resection. WHO grade I meningiomas show a recurrence rate between 7.25% - 23%. Atypical meningiomas (WHO grade II) between 29%-52%. Anaplastic meningiomas (WHO grade III) between 50%-94%. From recent studies the Wnt pathway is emerging as involving growth and progression of meningioma. However, molecular mechanism driving meningioma invasion and growth is unknown. (Desc. The gene Dkk-3 (Dickkopf-3, Wnt pathway inhibitor 3) encodes one of Dickkopf-related protein family of proteins. The activity of this gene is a tumor-suppressive type. The Dkk-3 protein (Dickkopf-related protein 3) is involved in embryonic development through its interactions with the WNT. The REIC/Dkk-3 expression has been shown to be down-regulated in various cancer cell lines. Aim of our study was to study the role of Dkk-3 expression and claudin-5 in meningiomas of different histotype and histological grade. Material and METHODS: We evaluated how meningiomas modify Dkk-3 expression in 20 tumors biopsies assessing both immunohistochemistry and western blotting. The tissue samples were embedded in paraffin for immunohistochemical analysis. The expression strength was analyzed and graded based on the positive ratio and intensity of immunoreactivity. The molecular analyses were performed on frozen sections of tumors through Western Blot method. Statistical analysis was also performed. RESULTS: The expression of Dkk-3 protein and claudin-5 were significantly reduced in meningioma samples compared to controls. These results were confirmed by immunohistochemistry revealing a slight expression of Dkk-3 protein in meningioma samples examined. It was also highlighted an irregular positivity of claudin-5 protein, on vascular localization. Claudin-5 levels were inversely regulated in meningiomas proteic extract with decreased levels in highly grade meningiomas. We found that REIC/Dkk-3 protein has been shown to mediate potent anti-tumor effects including reduced cell proliferation, independent growth, invasion and metastasis, and induced cancer cell specific apoptosis. Our preliminary results can suggest that meningiomas (Dkk-3 and Claudin grade III resections) and/or permanent, partly severe cranial nerve deficits. Stereotactic radiosurgery (SRS) has evolved as alternative first-line treatment for SCM. Here, we report about the long term clinical and radiological follow-up of an unique cohort of patients with SCM treated with LINAC based SRS. MATERIAL AND METHODS: In this single center retrospective study we analyzed 22 patients with SCM who underwent single fraction LINAC SRS between 1993 and 2012 and had a minimum follow-up of 3 months. We evaluated tumor control (no further intervention needed) by the Kaplan-Meier method. Additionally, patient data were analyzed in terms of clinical symptom control and incidence of complications or unexpected side effects rated by Common Terminology Criteria for Adverse Events (CTCAE; v4.03). RESULTS: 82 patients with meningioma (f/m:62/20, median age 51 years, range 33-81 years) were identified. Mean tumor volume was 5.8 ± 3.5 cm³ (range, 0.6-16 cm³), the mean marginal dose was 12 ± 2.2 Gy (range, 7.0-18.75 Gy) at isodose levels of 64 ± 17% (range, 40-85%). Median follow-up (FU) was 57 months (range, 3-226 months). Tumor control was 100% after 6 and 12 months, 97% after 5-years and 94% after 10-years. Symptomatic response was not correlated with CSM status. The survival rate after 1, 5, and 10 years was 97%, 94% and 91%, respectively. CONCLUSIONS: SRS for SCM provides reliable long term tumor control without considerable permanent side effects. Thus, SRS should be taken into account when counselling patients harbouring CSM.

**P12.02 PROTEOME AND PHOSPHOPROTEOME ANALYSIS IDENTIFIES STAT1 AS A NOVEL TARGET IN DIFFERENT GRADE MENINGIOMAS**

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Meningiomas are slow growing tumours of the meninges that affect brain and spinal cord. They account for a quarter of all primary brain tumours of the central nervous system. Accordingly to the WHO classification system, meningiomas are classified as grade I, atypical grade II and malignant grade III. Symptoms include headaches, focal neurological signs depending on localisation and seizures. The standard of treatment for these tumours is (radio)surgery. Nevertheless, it is estimated that one third of meningiomas cannot be operated or can be only partially resected, often with significant morbidity. Current chemotherapies are not effective therefore it is a great medical need to find novel therapeutic options. We aim to identify novel targets/biomarkers by analysing proteome and phosphoproteome of different grade meningioma tumour specimens in addition. Meningioma-derived primary tumour cells were analysed by mass spectrometry to decipher proteome and phosphoproteome. Phosphoproteins were isolated by an additional purification step. Overall we analysed 22 meningiomas (8 grade I, 8 grade II and 6 grade III) for the proteome and 14 for the phosphoproteome (5 grade I, 5 grade II and 4 grade III). Comparative studies were performed to identify aberrantly overexpressed proteins and dysregulated pathways compared to healthy human meninges (N=3). Among the proteins found significantly upregulated in meningioma vs. normal controls we identified STAT1, a member of the JAK/STAT signalling pathway. Validation studies performed on primary meningioma cells confirmed that the total amount of the protein was overexpressed four times compared to normal human meningeal cells. Additionally, both phosphorilation sites (Y701 and S277) on STAT1 were aberrantly activated in meningioma cells but not in meningeal cells. Immunohistochemical analysis confirmed an upregulation of phosphorylated STAT1(Y701) especially on grade III meningiomas, in agreement with expression studies, although with high variability across samples. When the Jak/STAT signalling pathway gets activated in response to cytokines and growth factors, STAT1 is phosphorylated by activated JAKs and translocate into the nucleus to regulate gene expression. In primary meningioma cells we found that the amount of phosphorylated STAT1 promi-

**P12.07 LONG TERM FOLLOW-UP OF CAVERNOUS SINUS MENINGIOMAS AFTER STEREOTACTIC RADIOSURGERY**

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**INTRODUCTION:** Microsurgical resection of cavernous sinus meningiomas (CSM) is challenging with a high percentage of recurrence due to incomplete resection (>10% reported recurrence rate after Simpson grade I-II resection) and >20% after Grade III resection. The disease is often challenging due to multiple localisations and complex cranial nerve deficits. Stereotactic radiosurgery (SRS) has evolved as alternative first-line treatment for CSM. Here, we report about the long term clinical and radiological follow-up of an unique cohort of patients with CSM treated with LINAC based SRS. MATERIAL AND METHODS: In this single center retrospective study we analyzed 22 patients with CSM who underwent single fraction LINAC SRS between 1993 and 2012 and had a minimum follow-up of 3 months. We evaluated tumor control (no further intervention needed) by the Kaplan-Meier method. Additionally, patient data were analyzed in terms of clinical symptom control and incidence of complications or unexpected side effects rated by Common Terminology Criteria for Adverse Events (CTCAE; v4.03). RESULTS: 82 patients with meningioma (f/m:62/20, median age 51 years, range 33-81 years) were identified. Mean tumor volume was 5.8 ± 3.5 cm³ (range, 0.6-16 cm³), the mean marginal dose was 12 ± 2.2 Gy (range, 7.0-18.75 Gy) at isodose levels of 64 ± 17% (range, 40-85%). Median follow-up (FU) was 57 months (range, 3-226 months). Tumor control was 100% after 6 and 12 months, 97% after 5-years and 94% after 10-years. Symptomatic response was not correlated with CSM status. The survival rate after 1, 5, and 10 years was 97%, 94% and 91%, respectively. CONCLUSIONS: SRS for SCM provides reliable long term tumor control without considerable permanent side effects. Thus, SRS should be taken into account when counselling patients harbouring CSM.