TERT Promoter Mutation Status in Meningioma

Increasing evidence suggests that genomic and molecular markers need to be integrated into meningioma grade. Telomerase reverse transcriptase promoter (TERTp) mutation is receiving attention due to its clinical relevance in meningioma treatment. The predictive ability of conventional and diffusion MRI parameters for determining the TERTp mutation status in World health organization grade 2 meningiomas has yet been identified.

In a study, from the Yonsei University College of Medicine, Seoul, 63 patients with surgically confirmed grade II meningiomas (56 TERTp wildtypes, 7 TERTp mutants) were included. Conventional imaging features were qualitatively assessed. The maximum diameter, the volume of the tumors, and histogram parameters from the apparent diffusion coefficient (ADC) were assessed. Independent clinical and imaging risk factors for TERTp mutation were investigated using multivariable logistic regression. The discriminative value of the prediction models with and without imaging features was evaluated.

In the univariable regression, older age (odds ratio [OR] = 1.13, P = 0.005), larger maximum diameter (OR = 1.09, P = 0.023), larger volume (OR = 1.04, P = 0.014), lower mean ADC (OR = 0.02, P = 0.025), and lower ADC 10th percentile (OR = 0.01, P = 0.014) were predictors of TERTp mutation. In multivariable regression, age (OR = 1.13, P = 0.009) and ADC 10th percentile (OR = 0.01, P = 0.038) were independent predictors of variables for predicting the TERTp mutation status. The performance of the prediction model increased upon inclusion of imaging parameters (area under the curves of 0.86 and 0.91, respectively, without and with imaging parameters).

Older age and lower Apparent diffusion coefficient 10th percentile may be useful parameters to predict TERT Promoter Mutation in World health organization grade 2 meningiomas [1].

A consecutive single-center cohort of 40 patients with malignant meningioma (WHO grade III) treated between 2000 and 2018, including specimens from primary and secondary malignant meningiomas with the corresponding earlier benign specimens and later malignant recurrences. In total 107 tumor samples were studied by Sanger sequencing for TERT promoter mutational status.

Seven of 40 patients (17.5%) harbored TERTpMut thus validating the incidence of TERTpMut in previous non-population-based cohorts. In 6/7 patients, the TERTpMut was present at initial surgery (WHO grade I-III) while in one patient the TERTpMut was found de novo when the meningioma became malignant. The incidences were 2/1.000.000/year for TERTpMut WHO grade III meningioma and 8/1.000.000/year for TERTpwt WHO grade III meningioma in our catchment area. We found a 1.7 times higher recurrence rate (CI 95% 0.65-4.44) and a 2.5 higher mortality rate per 10 person-years (CI 95% 1.01-6.19) for TERTpMut compared to TERTpwt.

TERTpMut can occur independently of malignant progression in meningioma and was most often present from the first tumor sample across recurring tumors. TERTpMut in WHO grade III may represent a marker of an aggressive subset of tumors [2].

From 110 meningioma patients, 128 tissue samples were analyzed for the TERT promoter mutations C228T and C250T by direct sequencing. Of the 128 samples, 121 were tested for cell propagation in vitro. Telomerase activity, TERT mRNA expression, and telomere lengths were investigated by telomeric repeat amplification protocol assay, reverse transcription PCR, and quantitative PCR, respectively. Impact of the E-twenty-six (ETS) transcription factor inhibitor YK-4-279 on cell viability and TERT promoter activity was analyzed.

Results: TERT promoter mutations were found in 5.5% of all samples analyzed and were associated with a significantly upregulated telomerase activity and TERT mRNA expression ($P < 0.0001$ both). Regarding telomere lengths, no significant difference between the TERT promoter wild-type and mutated subgroups was detected. Patients with TERT promoter mutated tumors exhibited significantly shorter overall survival ($P = 0.0006$; 53.8 vs 115.6 mo). The presence of TERT promoter mutations but not telomerase activity or TERT mRNA expression predicted indefinite cell growth in vitro. TERT promoter mutated meningioma cells were hypersensitive against the ETS transcription factor inhibitor YK-4-279, inducing a distinct downregulation of TERT promoter activity.

Conclusion: TERT promoter mutations drive meningioma aggressiveness, resulting in reduced patient survival, but might also open novel therapeutic options for progressive disease [3)].

Goutagny et al., sequenced the TERT promoter in 85 meningiomas from 73 patients. We found a high incidence of TERT promoter mutations in patients with meningiomas undergoing malignant histological progression (28%, n = 5/18 patients). In this subset of patients with histological progression, TERT promoter mutations were found in both the lowest and the highest grade tumors, and in both NF2-mutated and nonmutated samples. In contrast, one mutation was identified in 35 meningiomas without recurrence or progression, belonging to various histological grades. This sample was an aggressive meningioma in a patient who died shortly after surgery. Interestingly, tumors showing relapse without histological progression were not mutated for TERT promoter (n = 20). Finally, TERT promoter mutations were associated with a marked increase in TERT expression. Thus, TERT promoter mutations are pivotal genetic alterations involved in malignant progression of meningiomas and could be used as a biomarker to identify meningiomas at risk of malignant transformation [4)].

---

hTERT promoter methylation was analyzed in 78 meningiomas and 38 meningeal hemangiopericytoma samples by methylation-specific polymerase chain reaction (MS-PCR) and compared with histopathological and clinical variables and with immunohistochemical hTERT expression. Promoter methylation was found in 62 samples (53 %) and tended to be higher in meningiomas (N = 19/41, 46 %) than in hemangiopericytomas (N = 8/33, 24 %, p = .057). In meningiomas, methylation was 16, 60 and 77 % in grade I, II and III tumors (p < .001) and higher in recurrent (N = 33/37, 89 %) than in primary diagnosed (N = 19/41, 46 %) tumors (OR 5.14, 95 % CI 1.34-19.71, p = .017). Univariate analyses showed shorter mean progression free and overall survival in methylated than in unmethylated individuals (26 vs. 100 months; p = .045 and 110 vs. 113 months; p = .025, respectively). Moreover, hTERT expression was found in 70 % (N = 53) and was more frequent in methylated than in unmethylated samples (78 vs. 52 %, OR 3.36, 95 % CI 1.20-9.40, p = .021). In hemangiopericytomas, methylation was similar in grade II (24 %) and III (25 %, p > .05) and in primary (24 %) and recurrent tumors (40 %, p > .05). hTERT expression was similar as compared to meningiomas (74 %, N = 28, p > .05) but was independent of promoter methylation (OR

4.26, 95 % CI 0.47-39.0, p = .199). In meningeal tumors, hTERT promoter methylation is more common than mutations and in meningiomas but not in hemangiopericytomas positively correlated with WHO grade and hTERT expression [5].

References

1)
Shin I, Park YW, Ahn SS, Kang SG, Chang JH, Kim SH, Lee SK. Clinical and Diffusion Parameters may Noninvasively Predict TERT Promoter Mutation Status in Grade II Meningiomas. J Neuroradiol. 2021 Mar 11:S0150-9861(21)00056-0. doi: 10.1016/j.neurad.2021.02.007. Epub ahead of print. PMID: 33716047.

2)
Maier AD, Stenman A, Svahn F, Mirian C, Bartek J Jr, Juhler M, Zedenius J, Broholm H, Mathiesen T. TERT promoter mutations in primary and secondary WHO grade III meningioma. Brain Pathol. 2021 Jan;31(1):61-69. doi: 10.1111/bpa.12892. Epub 2020 Sep 15. PMID: 32805769.

3)
Spiegl-Kreinecker S, Lötsch D, Neumayer K, Kastler L, Gojo J, Pirker C, Pichler J, Weis S, Kumar R, Webersinke G, Gruber A, Berger W. TERT promoter mutations are associated with poor prognosis and cell immortalization in meningioma. Neuro Oncol. 2018 Nov 12;20(12):1584-1593. doi: 10.1093/neuonc/noy104. PMID: 30010853; PMCID: PMC6231195.

4)
Goutagny S, Nault JC, Mallet M, Henin D, Rossi JZ, Kalamarides M. High incidence of activating TERT promoter mutations in meningiomas undergoing malignant progression. Brain Pathol. 2014 Mar;24(2):184-9. doi: 10.1111/bpa.12110. PubMed PMID: 24261697.

5)
Fürtjes G, Köchling M, Peetz-Dienhart S, Wagner A, Heß K, Hasselblatt M, Senner V, Stummer W, Paulus W, Brokinkel B. hTERT promoter methylation in meningiomas and central nervous hemangiopericytomas. J Neurooncol. 2016 Oct;130(1):79-87. PubMed PMID: 27465278.