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TERT Promoter Mutations in Progressive Treatment-resistant Meningiomas

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Introduction

Recurrent meningiomas often undergo a grade-progression to become atypical or malignant upon recurrence. Detailed study of progressive meningioma has been hampered by the lack of available paired specimens. Here, we sequenced the TERT promoter (TERTp) in a large series of patients with treatment-resistant meningiomas at initial diagnosis as well as their sequential recurrences.

Methods

We scored 77 meningiomas from 36 patients for TERTp mutations. All patients in this study developed recurrences during the median follow-up of 13.3 years (range 6.4 - 25.5 years) and underwent three surgeries on average (range 2-8). Additionally, we screened geographically distinct sites of all TERTp-mutant meningiomas to interrogate intratumoral heterogeneity.

Learning Objectives

By the conclusion of this session, participants should be able to recognize the clinical importance of TERTp mutations in meningioma genesis and its impact on patient's survival

Results

TERTp mutations were detected in 18 tumor samples (18/77= 23.3%) from 12 patients, but not in any of the matched blood sample DNAs, excluding germline mutations. Notably, the TERTp mutations were absent in the initial lower-grade tumor and were present in the subsequent recurrent tumors. Moreover, we observe emergent spatial heterogeneity in the form of mixed populations of recurrent tumor cells containing different mutation status of the TERT promoter gene in three cases. Patients with emergence of TERTp-mutant meningiomas had a significantly shorter overall survival than their TERTp wild-type counterparts, when measured from the time of initial diagnosis (2.4 vs 11.1 years, 95% CI 0.25-4.54 vs 9.3- 16.8 years p= 0.007).

Conclusions

Our data confirm the high frequency of TERTp mutations and the emergence of TERT promoter mutation in recurrent progressive meningiomas, strongly indicating the presence of ongoing evolution impacting the natural history of these tumors. TERTp mutations are mostly associated with poor outcome. Finally, our study provides important insight into the complexity of tumor heterogeneity and has important implications for targeted therapy in treatment-resistant meningiomas.

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