Title: Telomerase reverse transcriptase promoter mutations in a cohort of adult gliomas – Clinicopathological correlates.

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Introduction

Gliomas are a heterogeneous group of neoplasms that comprise almost 70% of all primary central nervous system (CNS) neoplasms. While these tumours were previously classified on the basis of their histology, with the advent of molecular markers that provide enhanced diagnostic accuracy and prognostic information, the classification of CNS tumors now includes phenotypic and genotypic parameters. This is evidenced in the 2016 update of the WHO classification of CNS tumours which incorporates IDH mutations and 1p/19q co-deletions into the classification of gliomas. In recent years it has been found that TERT promoter mutations are of prognostic relevance in gliomas.

Objectives

1)To determine the prevalence of TERT promoter mutations in diffuse gliomas of WHO grades II, III and IV.
2) To determine the association of TERT promoter mutations with other molecular alterations in diffuse gliomas.
3) To assess the role of TERT promoter mutations in overall survival and progression free survival in relation to histological and molecular glioma subtypes.

Materials and methods

All gliomas of WHO grade II, III and IV diagnosed in the Department of General Pathology in the time period January 1st 2009 to January 2012 that had tissue in the tumour bank were traced in the registry. Clinical details of these patients was retrieved that included age, gender, size, presenting symptoms, MRI features, location of tumor surgical treatment given, chemotherapy status, radiotherapy status, recurrence and death.
The histological features of each of these cases was reviewed. For those cases that had not had the complete panel of ancillary tests for arriving at a specific diagnosis, representative slides were selected and sections cut from their corresponding paraffin blocks. 2 to 3-micron thick sections from these selected paraffin blocks were cut and mounted on Poly-L lysine coated for immunohistochemistry for IDH-1 mutation and ATRX mutation and FISH for 1p/19q co-deletions. PCR sequencing for TERT promoter mutation. Five glioma molecular sub groups of gliomas were defined using three molecular alterations - TERT promoter mutations, IDH

mutation, and 1p/19q codeletion. The molecular sub-groups were: i) IDH mutations only, ii) IDH and TERT mutations only, iii) IDH and 1p/19q co-deletion only, iv) Triple negative and v) Triple positive.

Results

A cohort of 107 adult patients with diffuse gliomas, WHO grades II-IV, formed the study group IDH mutations were seen in 62% of diffuse gliomas, and their presence was significantly associated with a better progression free and overall survival(p=0.001). 1p/19q co-deletions were significantly associated with better overall and progression free survival (p=0.028). TERT promoter mutations were seen in 47.6% and occurred frequently in Anaplastic oligodendrogliomas (94%), Oligodendrogliomas (87.5%) and Glioblastomas (54%). There was no statistical correlation seen between TERT promoter mutations and survival. However, analysis of the molecular sub-groups showed that the triple positive tumours carried the best prognosis, followed by 'IDH only', triple negative and finally 'TERT only' tumours (p-value <0.000).

Conclusion

Sub-classification of diffuse gliomas using molecular markers, TERT promoter mutations, IDH mutation, and 1p/19q codeletion, separates them into prognostically relevant categories