Brief Communication

TERT promoter status does not add prognostic information in IDH-wildtype glioblastomas fulfilling other diagnostic WHO criteria: A report of the RANO resect group

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In IDH-wildtype glioblastomas which meet the histopathological or molecular diagnosis criteria, it remains unclear whether the presence of TERT promoter mutations provides additional prognostic information. Based on a multicenter cohort of 466 IDH-wildtype glioblastomas (including 396 with and 70 patients without TERT promoter mutations), we found that TERT promoter mutations were neither associated with progression-free survival nor overall survival. This held true in various treatment-based or molecular subgroups. This argues against standardized analysis for TERT promoter mutation status for the purpose of prognostic or therapeutic relevance in newly diagnosed IDH-wildtype glioblastoma that otherwise meets the histopathological and molecular diagnosis criteria.

The WHO 2021 classification restricts the diagnosis of “glioblastoma WHO grade 4” to IDH-wildtype astrocytic gliomas either with (1) classical histopathological hallmarks or (2) qualifying molecular features. The latter include EGFR amplification, +7/−10 genotype, and TERT promoter mutation which are all associated with less favorable outcome when observed in combination with IDH-wildtype status. Whether TERT promoter mutations are of prognostic value in IDH-wildtype glioblastomas which otherwise yet fulfill the diagnostic (histopathological or molecular) criteria for glioblastoma is unclear. Here, we explored such an association based upon a well-annotated glioblastoma cohort from 7 international neuro-oncological centers participating in the RANO resect group. With approval of the ethics committee of the Ludwig-Maximilians-University (Munich, Germany; AZ-21-0996), the RANO resect group compiled a retrospective database of newly diagnosed IDH-wildtype glioblastomas treated between 2003 and 2022 with a follow-up of ≥3 months. For the current study, individuals were selected when information on...
**TERT** promoter mutation status was available for review. Demographics, molecular information, clinical data, and outcome were extracted; and date of progression was determined per RANO criteria.

Among 1008 **IDH**-wildtype glioblastomas WHO grade 4, **TERT** promoter status was available in 466 patients including 396 individuals with **IDH**/**TERT** and 70 patients without **TERT** promoter mutations (**IDH**/**TERT**). Diagnosis rested upon **IDH**-wildtype combined with histopathological findings in 372 **IDH**/**TERT** (93.9%) and 65 **IDH**/**TERT** patients (92.9%); and was established based on the molecular signature (**TERT** promoter mutation for **IDH**/**TERT**, **EGFR** amplification for **IDH**/**TERT**), in the absence of classical histological findings in the remaining patients. Three hundred and fifty-eight **IDH**/**TERT** (90.4%) and 63 **IDH**/**TERT** patients (90%) underwent microsurgical resection, whereas the remaining had biopsy for tissue-based diagnosis. There were no differences in **MGMT** promoter methylation status, first-line therapy, or pre- and postoperative tumor volumes (both for contrast-enhancing and noncontrast-enhancing tumor) between **IDH**/**TERT** and **IDH**/**TERT** patients (Figure 1A and B). Median progression-free survival was 8 months and overall survival was 18 months at a median follow-up time of 36 months (**IDH**/**TERT** vs **IDH**/**TERT**: 33 vs 52 months; HR: 1.50, CI: 1.0–2.3). When patients were stratified according to **TERT** promoter mutation status, no outcome differences were detected for progression-free survival (**IDH**/**TERT** vs **IDH**/**TERT**: 7 vs 8 months; HR: 1.03, CI: 0.8–1.4) or overall survival (**IDH**/**TERT** vs **IDH**/**TERT**: 18 vs 17 months; HR: 0.97, CI: 0.7–1.3) (Figure 1C). Also, no association between survival and **TERT** promoter mutation status was found in the subgroups of patients with **MGMT** promoter methylation (HR for **IDH**/**TERT**: 0.99, CI: 0.6–1.8), unmethylated **MGMT** promoter status (HR for **IDH**/**TERT**: 0.92, CI: 0.5–1.7), first-line radiochemotherapy per EORTC 26981/22981 (HR for **IDH**/**TERT**: 1.00, CI: 0.7–1.4), or classical histopathological findings of glioblastoma (HR for **IDH**/**TERT**: 1.06, CI: 0.8–1.5).

We did therefore not find evidence that **TERT** promoter status adds prognostic information in **IDH**-wildtype glioblastomas exhibiting classical histopathological hallmarks (or other mutations) sufficient for glioblastoma diagnosis. This is in line with previous reports on **IDH**-wildtype glioblastomas, although these studies have either not controlled for clinical and molecular confounders or were substantially limited in sample size. Notably, **IDH**/**TERT** glioblastomas may identify a subset with a distinct

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**Figure 1.** Clinico-molecular markers and outcome in **IDH**-wildtype glioblastoma with or without **TERT** promoter mutations. (A) Distribution of **MGMT** promoter methylation status (upper panel) and first-line therapies following surgery (lower panel) in **IDH**-wildtype glioblastomas with **IDH**/**TERT**, n = 396) or without **TERT** promoter mutations (**IDH**/**TERT**, n = 70). (B) Pre- (upper panel) and postoperative tumor volumes (lower panel) in cm³ among **IDH**-wildtype glioblastomas undergoing microsurgical tumor resection with **IDH**/**TERT**, n = 358; green) or without **TERT** promoter mutations (**IDH**/**TERT**, n = 63; blue). Volumes are indicated for contrast-enhancing (CE) and noncontrast-enhancing (nCE) tumor tissue. Median ± interquartile range. (C) Kaplan–Meier estimates of progression-free survival (left) and overall survival (right) for **IDH**-wildtype glioblastomas with (green line) or without **TERT** promoter mutations (blue line). Points indicate deceased or censored patients; light shadings indicate SEM.
(epi-)genetic and molecular profile compared to IDH<sup>wt</sup>/TERT<sup>mut</sup> tumors and may benefit from different, personal-
ized treatment strategies. These biological findings, how-
tever, to date do not result in different clinical out-
comes. Thus, up to now our retrospective data argue ag-
standardized analysis for TERT promoter mutation status for the purpose of prognostic or therapeutic rele-

vance in newly diagnosed IDH-wildtype glioblastoma that otherwise meets the histopathological and molecular di-
agnosis criteria. This might change in the future whenever TERT-directed therapies emerge.

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