TERT promotor 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 promotor mutations provides additional prognostic information. Based on a multicenter cohort of 466 IDH-wildtype glioblastomas (including 396 with and 70 patients without TERT promotor mutations), we found that TERT promotor 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 promotor 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 promotor mutation which are all associated with less favorable outcome when observed in combination with IDH-wildtype status. Whether TERT promotor mutations are of prognostic value in IDH-wildtype glioblastomas which otherwise 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 (IDHwt/TERTmut) and 70 patients without TERT promoter mutations (IDHwt/TERTwt). Diagnosis rested upon IDH-wildtype combined with histopathological findings in 372 IDHwt/TERTmut (93.9%) and 65 IDHwt/TERTwt patients (92.9%); and was established based on the molecular signature (TERT promoter mutation for IDHwt/TERTmut, EGFR amplification for IDHwt/TERTwt) in the absence of classical histological findings in the remaining patients. Three hundred and fifty-eight IDHwt/TERTmut (90.4%) and 63 IDHwt/TERTwt 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 IDHwt/TERTmut and IDHwt/TERTwt 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 (IDHwt/TERTmut vs IDHwt/TERTwt: 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 (IDHwt/TERTmut vs IDHwt/TERTwt: 7 vs 8 months; HR: 1.03, CI: 0.8–1.4) or overall survival (IDHwt/TERTmut vs IDHwt/TERTwt: 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 IDHwt/TERTmut: 0.99, CI: 0.6–1.8), unmethylated MGMT promoter status (HR for IDHwt/TERTwt: 0.92, CI: 0.5–1.7), first-line radiochemotherapy per EORTC 26981/22981 (HR for IDHwt/TERTmut: 1.00, CI: 0.7–1.4), or classical histopathological findings of glioblastoma (HR for IDHwt/TERTwt: 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, IDHwt/TERTwt glioblastomas may identify a subset with a distinct

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 (IDHwt/TERTmut, n = 396) or without TERT promoter mutations (IDHwt/TERTwt, n = 70). (B) Pre- (upper panel) and postoperative tumor volumes (lower panel) in cm³ among IDH-wildtype glioblastomas undergoing microsurgical tumor resection with (IDHwt/TERTmut, n = 358; green) or without TERT promoter mutations (IDHwt/TERTwt, 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\textsuperscript{wt}/TERT\textsuperscript{mut} tumors and may benefit from different, personalized treatment strategies.\textsuperscript{2,4,6} These biological findings, however, to date do not result in different clinical outcomes. Thus, up to now our retrospective data argue 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. This might change in the future whenever TERT-directed therapies emerge.

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**References**