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Implementation of TERT promoter mutations improve prognostication of the WHO classification in meningioma

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The WHO classifications of meningioma have been solely based on histological criteria up to now. However, evidence has emerged that (epi-)genomic classifications correlate better with clinical course than histological grading, and several molecular markers attenuate incongruences between clinical course and current WHO grading [1–4]. The inclusion of valid molecular biomarkers into the histological WHO grading system could therefore strengthen classification and prognostication of meningioma patients. We recently described an association between patients with a Telomerase reverse transcriptase (TERT) gene alterations and a poor prognosis irrespective of the WHO grade in a meta-analysis of individual patient data encompassing all hitherto published meningioma patients with such alterations [3]. Improvement of patient prognostication is a main goal for continuous refinement of the WHO classification. TERT gene alterations candidates as an attractive biomarker based on its unequivocal association with recurrence. However, implementation of any biomarker into WHO classifications should be supported by its ability to predict an event rather than an observed association. It, therefore, remains to be established whether TERT gene alterations lead to better prediction of prognosis, and therefore a more reliable classification, when implemented into WHO gradings. To address this crucial clinical question, we herein compared prognostic performance of the WHO classification with and without (w/o) inclusion of the most frequent gene alterations, i.e. the C228T and C250T TERT promoter mutations (TERTp-mut), while acknowledging that further rare gene alterations that affect TERT, exist (e.g. TERT gene rearrangements) [5–7].

The association with short- and long-term recurrence was evaluated using time since diagnosis as the underlying time scale. Time to recurrence was analysed with a competing risk approach, as recurrence-free death preclude the event of recurrence. Hence, we applied a recurrence-specific Cox proportional hazard regression to estimate the effect of WHO grade and TERTp-mut on the recurrence rate, where patients were censored at the time of recurrence-free death or end of follow-up. We compared two rivalling models to investigate if TERTp-mut improved the prognostic performance. The first model, abbreviated WHO w/o TERT, only included the WHO grade, while the second model, abbreviated WHO +TERT, included TERTp-mut in addition to the WHO grade. Both models were adjusted for age (at diagnosis) and stratified by the 2016 versus 2007 WHO classification of CNS tumours. The assumption of proportionality was evaluated with Schoenfeld residuals and found to be valid for all models.

We applied both WHO w/o TERT and WHO +TERT to predict the 5- and 10-year risk of recurrence, and subsequently compared the prognostic performance obtained by
the two models. Here, we used leave-one-out bootstrapping of 1,000 subsamples each comprising 410 patients randomly drawn with replacement. The prognostic performance of *WHO w/o TERT* and *WHO +TERT* was averaged based on the 1,000 subsamples, and evaluated using the area under the receiver operating characteristics curve (AUC, a higher score indicates a better model) and the Brier score (a lower score indicates a better model).

We compiled individual patient data from nine previously published cohorts, encompassing a total 717 meningioma patients [5,7–14]. We excluded patients (n = 21) with *TERT* gene alteration types other than C228T or C250T promoter mutations (including *Unknown* type). Patients with missing data on overall survival were also excluded. In total, 410 meningioma patients remained with data required for the competing risk analysis.

*TERT*mut affected 45 out of the 410 patients (12.3%), comprising 12 C250T and 33 C228T (73.3%) *TERT* promoter mutations, while the remaining 365 patients had the *TERT* promoter wild-type counterpart (*TERT*wt). In compilation, 50 WHO-1, 240 WHO-2 and 120 WHO-3 meningioma patients were included (Table 1). *TERT*mut occurred in 12.0% of WHO-1 (n=6/50), 8.3% of WHO-2 (n=20/220) and 15.8% of WHO-3 (n=19/120) meningioma samples. The 2007 WHO classification of CNS tumours were used to categorize 61 (14.9%) meningioma patients, while the remaining 349 patients were classified according to the 2016 edition (an overview is presented in Table 1). The entire cohort was followed for 1,549 person-years with a median follow-up of 30.3 months (range: 0.1–386.2).

*TERT* promoter status constitutes a crucial measure of risk of recurrence. In comparison to *TERT*wt patients, the recurrence rate was significantly 2.43 (95% CI: 1.67 – 3.55) times higher for *TERT*mut patients (Table 2A). Similarly, the 5-year cumulative incidence of recurrence was 43.8% (95% CI: 38.3 – 49.3) versus 73.7% (95% CI: 60.7 – 86.7) for *TERT*wt and *TERT*mut patients, respectively. As a consequence, implementation of the *TERT* promoter status improved the WHO classification’s predictive power of recurrence. The 5- and 10-year risk of recurrence for *TERT*wt patients were predicted similarly when applying both the *WHO +TERT* and *WHO w/o TERT* model. In contrast, predictions obtained on *TERT*mut patients were incongruent when comparing these two models, as the *WHO +TERT* predicted considerably higher risk of recurrence in comparison to *WHO w/o TERT* specifically for the *TERT*mut patients (Figure 1AC). Therefore, adding the *TERT* promoter status to the WHO classification improved the calibration, meaning a more consistent agreement between observed frequency of recurrence and predicted risk of recurrence (Figure 1BD). Consequently, *WHO +TERT* conveyed a
better measure of prognostication of recurrence, shown by significantly better AUC (p=0.03 and p=0.0003) for the 5- and 10-year predictions in comparison with WHO w/o TERT. This was supported by the Brier scores, for which the 10-year prediction showed a significant difference (p=0.0003), but not the 5-year prediction (p=0.09) - although in favour for WHO +TERT (Figure 1BD).

TERT promoter mutations exerted different effects across the WHO grades, meaning the hazard ratio for TERTp-mut versus TERTp-wt differed between each WHO grade (Table 2B). The hazard ratio was significantly higher for TERTp-mut patients in WHO-1 and -2 meningiomas with hazard ratio 3.50 (95% CI: 1.42 – 8.65) and 4.44 (95% CI: 2.58 – 7.63), respectively. However, TERTp-mut did not associate with a significantly higher recurrence rate in reference to TERTp-wt in WHO-3 meningiomas with a hazard ratio of 1.31 (95% CI: 0.72 – 2.39). There were no significantly different hazard ratios between WHO-1, and WHO-2 or -3 meningiomas within the group of TERTp-mut patients (Table 2B). As previously reported, the poor prognosis associated with TERTp-mut was independent of WHO grade [3].

TERTp-mut was already known to associate with a poor prognosis in terms of tumor recurrence and overall survival in meningioma patients [3]. Our results indicated that acquired TERTp-mut associated with a high recurrence rate in WHO-1 and -2, but not WHO-3, meningiomas. The presented results were based on a large cohort of meningioma patients, with the major strength of encompassing all previously published cohorts.

At present, there is an unmet need for reliable biomarkers improve prognostication of meningioma recurrence. Herein, we demonstrated that implementation of C228T/C250T TERTp-mut into the WHO classification predicted early and late tumor recurrence more accurately than the WHO w/o TERT counterpart. Our findings, therefore, provided robust support for implementation of C228T/C250T TERTp-mut into the upcoming 2021 edition of the WHO classification. Current Next Generation Sequencing panels of a large number of cancer subtypes already include TERT promoter mutations, thus facilitating ease of implementation into common neuropathological routines. Other genetic alterations, such as gene fusions, are infrequent and require extended genomic analyses to detect.
Our study limitations include that the patients were not consecutive. All cohorts comprised selected patients to some degree who were often included retrospectively on basis of aggressive clinical behaviour. Consequently, the prevalence of TERTp-mut reported herein is unlikely to reflect an unselected population and presumably explains the occurrence of TERTp-mut in as many as 12% WHO-1 meningiomas. Despite such selection bias, we consider the present patient volume sufficient to reflect the typical clinical course of the individual WHO grades regardless of TERTp-mut status. Ultimately, the decision if all meningioma samples should be analysed for TERTp-mut is a question of cost-efficiency and a value judgement: how many needs to be analysed to identify a patient who would benefit? TERTp-mut certainly occur in benign meningiomas, but to an unknown extent. The failure to detect these high-risk patients will erroneously allocate them to a treatment and follow-up algorithm designed for patients with benign lesions. Here, one important consideration encompasses the observation that TERTp-mut was significant in WHO-1 and -2 meningiomas, exclusively, while the outcome in WHO-3 meningiomas already was poor regardless of TERTp-mut status.

Finally, not all patients were classified according to the WHO 2016 edition. The only patient subset at risk of incongruent classification between the 2016 and 2007 edition, comprise the WHO-1 2007 patients with brain invasion. Approximately 3.7% (n=15) of the patients were classified according to the 2007 WHO-1 and could theoretically have been reclassified to 2016 WHO-2 for brain invasion. Despite that the 2007 WHO-1 proportion was small, we stratified the analysis for the 2016 and 2007 WHO classification. We, in addition, performed a sensitivity analysis (not shown here) by omitting the 15 patients with 2007 WHO-1 meningiomas, which did not alter the results. Reclassification of the 61 patients categorized according to the 2007 WHO classification would, therefore, not have affected the results [15].

In conclusion, adding C228T and C250T TERTp-mut status to the WHO classification improves prognostication in terms of detecting meningioma patients at risk of early and late recurrence. Our findings support the inclusion of TERTp-mut into the standard diagnostic work-up of meningioma.
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None

CONTRIBUTION

- **Conceptualization:** CM and TM
- **Data curation:** TAJ, FS, SSK, MP, AB, JCT, SG, LB, ADM, GBS, HB, DS, DPC and PKB
- **Formal analysis:** CM and KG
- **Investigation:** All
- **Methodology:** CM and KG
- **Project administration:** CM and TM
- **Writing:** All

ETHICAL STATEMENT

This study was based on already published and anonymized data.
REFERENCES


Figure 1. AC: The predicted 5- and 10-year risks of recurrence obtained from WHO w/o TERT versus WHO +TERT. The diagonal indicates no difference between the two rivaling models. BD: Calibration, i.e. the agreement between the predicted 5- and 10-year risks of recurrence and observed frequency of recurrence. The diagonal indicates a perfect calibration.
Table 1. Cohort characteristics stratified for *TERT* promoter status.

<table>
<thead>
<tr>
<th>WHO Classification 2016</th>
<th>TERT promoter wild-type (n = 365)</th>
<th>TERT promoter mutation (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO-1 (n = 30)</td>
<td></td>
<td>WHO-1 (n = 5)</td>
</tr>
<tr>
<td>WHO-2 (n = 187)</td>
<td></td>
<td>WHO-2 (n = 15)</td>
</tr>
<tr>
<td>WHO-3 (n = 93)</td>
<td></td>
<td>WHO-3 (n = 19)</td>
</tr>
<tr>
<td>WHO Classification 2007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO-1 (n = 14)</td>
<td></td>
<td>WHO-1 (n = 1)</td>
</tr>
<tr>
<td>WHO-2 (n = 33)</td>
<td></td>
<td>WHO-2 (n = 5)</td>
</tr>
<tr>
<td>WHO-3 (n = 8)</td>
<td></td>
<td>WHO-3 (n = 0)</td>
</tr>
</tbody>
</table>

| Promoter mutation       |                                    |                                 |
|-------------------------|                                    |                                 |
| NA                      |                                    | C228T (n = 33)                  |
|                         |                                    | C250T (n = 12)                  |

| 5-year cumulative incidence of recurrence (95% confidence interval) | 43.8% (38.3 – 49.3) | 73.7% (60.7 – 86.7) |
Table 2A. Recurrence-specific Cox proportional hazard regression stratified for WHO Classification (2016 ed. versus 2007 ed.).

<table>
<thead>
<tr>
<th></th>
<th>WHO +TERT Hazard ratio (95% CI)</th>
<th>WHO w/o TERT Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TERTp-wt Reference</td>
<td>NA</td>
</tr>
<tr>
<td>TERTp-mut</td>
<td>2.43 (1.67 – 3.55)</td>
<td>NA</td>
</tr>
<tr>
<td>WHO-1</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>WHO-2</td>
<td>0.94 (0.61 – 1.43)</td>
<td>0.88 (0.58 – 1.35)</td>
</tr>
<tr>
<td>WHO-3</td>
<td>2.05 (1.31 – 3.22)</td>
<td>2.14 (1.37 – 3.42)</td>
</tr>
<tr>
<td>Age (per 1-year increase)</td>
<td>1.01 (0.99 – 1.02)</td>
<td>1.01 (0.99 – 1.02)</td>
</tr>
</tbody>
</table>
Table 2B. Recurrence-specific Cox proportional hazard regression stratified for WHO Classification (2016 ed. versus 2007 ed.) with effect modification between TERT\text{p-mut/p-wt} and WHO grade.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Hazard ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 1-year increase)</td>
<td>1.01 (1.00 – 1.02)</td>
</tr>
<tr>
<td>WHO-1</td>
<td>Reference</td>
</tr>
<tr>
<td>WHO-2</td>
<td>1.15 (0.45 – 2.96)</td>
</tr>
<tr>
<td>WHO-3</td>
<td>0.91 (0.34 – 2.45)</td>
</tr>
<tr>
<td>TERT\text{p-wt in WHO-1}</td>
<td>Reference</td>
</tr>
<tr>
<td>TERT\text{p-mut in WHO-1}</td>
<td>3.50 (1.42 – 8.65)</td>
</tr>
<tr>
<td>TERT\text{p-wt in WHO-2}</td>
<td>Reference</td>
</tr>
<tr>
<td>TERT\text{p-mut in WHO-2}</td>
<td>4.44 (2.58 – 7.63)</td>
</tr>
<tr>
<td>TERT\text{p-wt in WHO-3}</td>
<td>Reference</td>
</tr>
<tr>
<td>TERT\text{p-mut in WHO-3}</td>
<td>1.31 (0.72 – 2.39)</td>
</tr>
</tbody>
</table>