REVIEW

# Poor prognosis associated with TERT gene alterations in meningioma is independent of the WHO classification: an individual patient data meta-analysis

Christian Mirian ,[1] Anne Katrine Duun-Henriksen,[2] Tareq Juratli,[3,4] Felix Sahm,[5,6] Sabine Spiegl-Kreinecker,[7] Matthieu Peyre,[8] Annamaria Biczok,[5,9] Jörg-Christian Tonn,[5,9] Stéphane Goutagny,[10] Luca Bertero,[11] Andrea Daniela Maier,[1] Maria Møller Pedersen,[1] Ian Law,[12] Helle Broholm,[13] Daniel P. Cahill,[3] Priscilla Brastianos,[14] Lars Poulsgaard,[1] Kåre Fugleholm,[1] Morten Ziebell,[1] Tina Munch,[1,15,16] Tiit Mathiesen[1,16,17]

For numbered affiliations see end of article.

**Correspondence to**
Dr Christian Mirian, Department of Neurosurgery, Copenhagen 2100, Denmark; christian.mirian.larsen@regionh.dk

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## ABSTRACT

**Background** *TERT* gene alterations (*TERT*-alt) have been linked to increased risk of recurrence in meningiomas, whereas the association to mortality largely remain incompletely investigated. As incongruence between clinical course and WHO grade exists, reliable biomarkers have been sought.

**Methods** We applied the Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data Statement. We compiled data from eight studies and allocated patients to *TERT*-alt (n=59) or *TERT* promoter wild-type (*TERT*p-wt; n=618). We compared the two groups stratified for WHO grades as: incidence rates, survival probabilities and cumulative recurrences. We estimated the effects of WHO grade, age at diagnosis and sex as HRs.

**Results** *TERT*-alt occurred in 4.7%, 7.9% and 15.4% of WHO-I/WHO-II/WHO-III meningiomas, respectively. The median recurrence-free survival was 14 months for all *TERT*-alt patients versus 101 months for all *TERT*p-wt patients. The HR for *TERT*-alt was 3.74 in reference to *TERT*p-wt. For all *TERT*-alt patients versus all *TERT*p-wt patients, the median overall survival was 58 months and 160 months, respectively. The HR for *TERT*-alt was 2.77 compared with *TERT*p-wt. *TERT*-alt affected prognosis independent of WHO grades. Particularly, the recurrence rate was 4.8 times higher in WHO-I/-II *TERT*-alt patients compared with WHO-III *TERT*p-wt patients. The mortality rate was 2.7 times higher in the WHO-I and WHO-II *TERT*-alt patients compared with WHO-III *TERT*p-wt patients.

**Conclusions** *TERT*-alt is an important biomarker for significantly higher risk of recurrence and death in meningiomas. *TERT*-alt should be managed and surveilled aggressively. We propose that *TERT*-alt analysis should be implemented as a routine diagnostic test in meningioma and integrated into the WHO classification.

**Trial registration number** PROSPERO: CRD42018110566.

## BACKGROUND

Cell immortalisation and senescence escape, which is mainly caused by telomere maintenance, are hallmarks of cancer. The enzyme telomerase, a specialised DNA polymerase that adds telomere repeat segments to the ends of telomeric DNA, actively counteracts the telomere shortening.[1] The telomerase enzymatic subunit telomerase reverse transcriptase (*TERT*) is transcriptionally inactive in most non-neoplastic cells, whereas reactivation may induce cell immortalisation. It has been proposed that 90% of cancers express functionally significant levels of telomerase and that 73% of cancers demonstrate *TERT* gene alterations (*TERT*-alt), including promoter mutations, gene translocations and DNA amplifications.[2]

The WHO grading system classifies meningiomas based on histopathological morphology.[3] The main parameters are the number of mitoses per 10 high power field along with other more subjective criteria,[3 4] which yields a risk of interobserver bias.[5] There are examples of incongruence between the WHO grade and clinical course, in which low grade meningiomas rendered a poorer prognosis than higher grades of meningiomas in terms of recurrence-free survival.[6] As the current WHO grading system is not sufficient to predict the clinical course, reliable biomarkers have been sought. A particularly interesting target are *TERT*-alt including promoter mutations[5 7–11] and gene translocations.[12]

*TERT* mutations occur in specific 'hotspots' of the promoter (*TERT*p) region known as C228T and C250T (chromosomal positions 1,295,228 and 1,295,250). These C>T transition mutations result in new binding sites for a specific transcription factor family known as E-twenty-six (ETS), which leads to maintenance of the telomere length as binding of ETS-transcription factors is involved in the upregulation of *TERT* expression.[5 11 13] Similarly, genomic rearrangements that have led to *LPCAT1-TERT* and *RETREG1-TERT* fusions also upregulate TERT expression.[8 12] Genomic rearrangements that

associate with increased *TERT* expression and telomerase activity are seen in solid cancers, such as melanoma,[14] follicular-derived thyroid and bladder cancer,[15] other CNS malignancies[16 17] and thus represent a major biological hallmark of cancer.[1]

The incidence of *TERT*-alt has not yet been studied in consecutively collected meningioma tumour samples, but ranges from 6.3% to 9.8% in the largest cohorts hitherto investigated.[5 7 10 11] Interestingly, all previous studies consistently show a higher risk of recurrence in patients with *TERT*-alt meningiomas compared with their wild-type (*TERT*p-wt) counterpart, but the majority of these studies have incompletely discussed other clinically important differences, such as survival effects and patient characteristics, primarily due to small study cohorts.

When considering that meningioma is the most common intracranial neoplasm with an annual incidence of 7.8 per 100 000 inhabitants,[18] *TERT*-alt may affect a large population. While up to 80% of meningiomas can be cured through surgery, more than 20% of the patients experience a recurrence and progressive tumour behaviour.[5 19–23] Focusing on this subgroup, it is of high priority to unfold the prognostic implications of *TERT*-alt comprehensively.

Our primary objectives were to: first, report recurrence and mortality rates, and second, investigate risk of recurrence and death in *TERT*-alt versus *TERT*p-wt meningioma patients in general and in subgroups of WHO grades ranging from I to III. Our secondary objectives were to report characteristics of *TERT*-alt patients and to investigate effect modification of *TERT*-alt by the patients' age, sex and WHO grade.

## METHODS

This study was a meta-analysis using individual patient data (IPD) from a set of relevant studies. The approach adhered to the Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data (PRISMA-IPD) Statement.[24]

We performed a search that consisted of the keywords 'TERT' or 'telomerase reverse transcriptase' in combination with 'meningioma'. We searched PubMed (n=70), Embase (n=97) and Cochrane (n=0), adding up to a total of 167 papers identified. Two authors duplicated and performed the search independently (CM and ADM). There was consensus on the identified papers and the extracted data.

We performed the initial search 1 September 2018 and was reperformed the 25 June 2019. This was because we invested considerable amount time in data synthesis and extraction since the initial search. We identified one additional paper published in between the two searches, which we consequently included (figure 1 depicts the search diagram).

Inclusion criteria comprised: first, a specific laboratory test of *TERT*-alt; second, histopathological confirmation of WHO grade; third, reporting of *both* recurrence status (yes/no/lost to follow-up) *and* recurrence-free survival time; *and/or* fourth, reporting of *both* survival status (alive/dead/lost to follow-up) *and* survival time.

Exclusion criteria comprised: first, evaluation of *TERT* in other contexts than genomic alterations; second, non-meningioma tumours; third, animal studies; and fourth, conference abstracts.

In total, eight studies were eligible.[5 7–12 25] We applied the 'one-stage' approach in the PRISMA-IPD Statement and contacted the corresponding authors of all eight studies requesting raw IPD. The process was successful, and we obtained IPD from all eight studies.

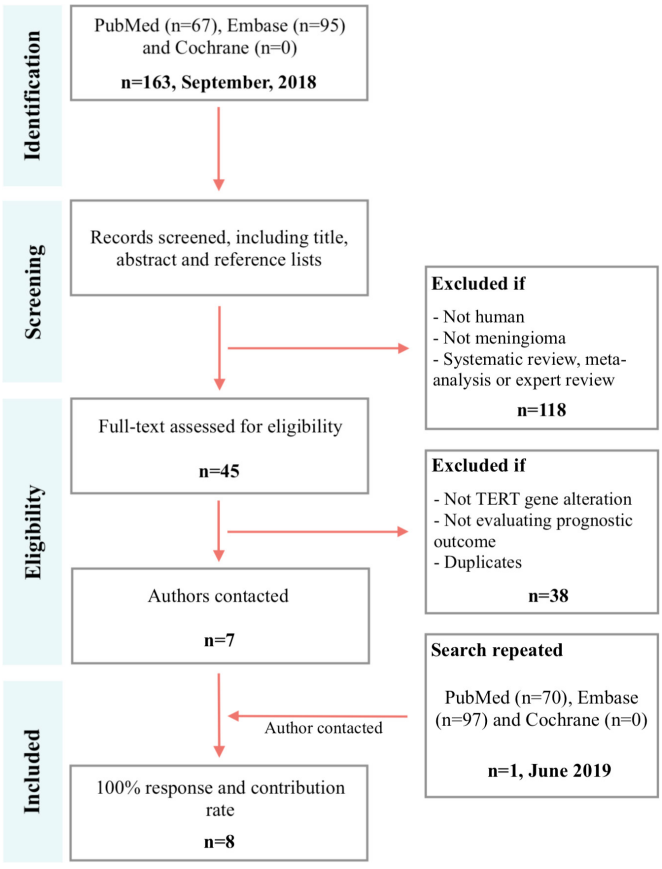


**Figure 1** Search diagram. TERT, telomerase reverse transcriptase.

We registered this study on PROSPERO and was published in its approved form on the 16 October 2018, following submission in September 2018.

We allocated patients into either *TERT*-alt or *TERT*p-wt. We chose the WHO grade at time of diagnosis as baseline, in case of multiple samples were collected. We excluded ineligible patients, which comprised: first, five patients in the Peyre *et al*[9] stud y as the baseline-WHO grade was unknown, and second, 21 patients from the Spiegl-Kreinecker *et al* study and 30 patients from the Bertero *et al* study due to missing recurrence-free and/or overall survival time.[11 25] In addition, it was not possible to retrieve age on *TERT*p-wt patients in one study.[12]

The IPD from each study did not necessarily contain all data needed to evaluate both recurrence *and* overall survival. Consequently, some patients were eligible for the analysis of both recurrence-free and overall survival, whereas others were included for only *one* of the analyses.

We estimated recurrence and mortality rates per 100 persons-years for different subgroups of WHO grades. The subgroups comprised: first, *TERT*-alt (all), that is, all WHO grades were combined in the *TERT*-alt group, *TERT*-alt (WHO-I and WHO-II) and *TERT*-alt (WHO-III), and second, *TERT*p-wt (all), that is, all WHO grades combined in the *TERT*p-wt group and *TERT*p-wt (WHO-III). Subsequently, we compared the incidence rates as ratios corresponding to the different subgroups mentioned above.

We estimated and plotted the survival probabilities for *TERT*-alt patients versus *TERT*p-wt patients in the subgroups described above. We applied the Kaplan-Meier method and the log-rank test for significance.

In the analyses of recurrence, we estimated the cumulative risk of recurrence while considering death *without* recurrence as a competing risk. Furthermore, we applied the Aalen-Johansen method to estimate the cumulative incidence and Gray's test to compare the curves.[26 27]

In addition, we applied a Cox regression model to investigate the association between the risk of either recurrence or death and age at diagnosis, sex, WHO grade and *TERT*-alt status. We reported the beforementioned covariates as: first, unadjusted estimates. We adjusted the estimates in the univariate analysis (only) to the effect from each individual centre ('centre effect'), to account for differences among the eight studies, whereas we adjusted the estimates in the multivariate analysis to the listed covariates and the centre effect. We tested non-linear effects for the continuous covariate *age at diagnosis* with restricted cubic splines and found that continuous covariate effect was linear. Thus, we included age at diagnosis as a linear continuous covariate.

We used time since diagnosis as underlying time scale. End of follow-up was either date of death, the date of lost to follow-up or the date of study termination in each individual study, whichever came first.

We evaluated the assumption of proportionality for all models with visual inspection of Schoenfeld residuals. We found that all covariate effects were proportional, except for sex in relation to both recurrence-free and overall survival. To accommodate this, we divided the time scale into two separate time periods: first, from 0 to 36 months, and second, from 36 months and onwards (in which the assumption was valid).

We applied a likelihood ratio test ($\chi^2$) to evaluate potential effect modification. We investigated interactions between the effect of *TERT*-alt and age at diagnosis, sex and WHO grade, respectively.

We considered p values equal to or below 0.05 significant.

We performed all analyses in R version 3.6.0[28] with the packages 'rms', 'survival', 'cmprsk' and 'etm'.[29–32] We visualised data using ggplot2 and metafor.[33 34]

## RESULTS

### Patients

We identified 167 papers, of which eight were eligible. The inclusion rate from all eligible studies was 100%. In total, we included data on 677 patients in our study. Of these, 667 and 527 patients were eligible for recurrence-free and overall survival analysis, respectively.

The pooled cohort of 677 patients comprised: 59 *TERT*-alt (all) patients and 618 *TERT*p-wt (all) patients; 169 WHO-I patients, 365 WHO-II patients and 143 WHO-III patients; the female (n=373) to male (n=304) ratio was 1.23. It was not possible to retrieve age from one of the studies,[12] but the mean age was 58 years based on the remaining seven studies (SD: 15.0, range: 6–89 years) (table 1A).

### *TERT*-alt patient characteristics

*TERT*-alt (all) comprised 60 *TERT*-alt in 59 *TERT*-alt patients, as one patient had synchronous mutations in C228T and C250T: comprising, 27 C228T, 11 C250T, one C228A, 18 not reported, 2 *RETREG1-TERT* fusions and 1 *LPCAT1-TERT* fusion. There were 8, 29 and 22 *TERT*-alt patients diagnosed with WHO-I, WHO-II and WHO-III meningioma, respectively. Hence, *TERT*-alt occurred in 4.7% of WHO-I meningiomas, 7.9% of WHO-II meningiomas and 15.4% of WHO-III meningiomas. In contrast to the entire pooled cohort, the female-to-male ratio had shifted to 0.74. *TERT*-alt was associated with patients' sex ($\chi^2$ test, p=0.05); in total, 7% of females and 11% of males had *TERT*-alt in the entire pooled cohort. The mean age was 60.8 years (SD: 12.5, range: 25–84 years), which was not significantly different from the mean age of 57.7 years (SD: 15.2, range: 6–89 years) among *TERT*p-wt patients in a two-sample t-test (p=0.08) (table 1B).

### Recurrence-free survival

The recurrence rate was 5.4 (95% CI 4.0 to 7.3) times higher in *TERT*-alt (all, n=59) patients compared with *TERT*p-wt (all, n=608) patients (figure 2). Including all WHO grades, the median recurrence-free survival was 14 months (95% CI 10 to 24) for *TERT*-alt (all) patients compared with 101 months (95% CI 90 to 124) for *TERT*p-wt (all) patients (log-rank test p<0.0001, figure 3A and table 1B).

By analysing data from patients with WHO grade III meningioma exclusively (n=140), the recurrence rate was 5.8 (95% CI 3.6 to 9.5) times higher for *TERT*-alt (WHO-III, n=22) patients than in their *TERT*p-wt (WHO-III, n=118) counterparts (figure 2). The median recurrence-free survival was 11 months (95% CI 9 to 28) for *TERT*-alt (WHO-III) patients versus 29 months (95% CI 23 to 60) for *TERT*p-wt (WHO-III) patients (log-rank test p=0.0015, figure 3B). In comparison between *TERT*-alt (WHO-I and WHO-II, n=37) patients and *TERT*p-wt (WHO-III, n=118) patients, we found that *TERT*-alt (WHO-I and WHO-II) patients rendered a 4.8 (95% CI 3.3 to 6.9) times higher recurrence rate (figure 2). Furthermore, the median recurrence-free survival was 16 months (95% CI 12 to 31) for *TERT*-alt (WHO-I and WHO-II) patients and 29 months (95% CI 23 to 60) for *TERT*p-wt (WHO-III) patients as mentioned above (log-rank test p=0.00096, figure 3C).

The effect of *TERT*-alt on recurrence-free survival was not modified by age at diagnosis ($\chi^2$ p=0.09), sex ($\chi^2$ p=0.7) or WHO grade ($\chi^2$ p=0.2).

### Cumulative incidence of recurrence

The 1-year and 2-year cumulative incidence of recurrence for *TERT*-alt (all) patients was 40.7% (95% CI 20.4% to 54.2%) and 63.4% (95% CI 51.2% to 75.6%), respectively, when considering death *without* recurrence a competing risk (figure 4A).

The cumulative incidence of recurrence for *TERT*p-wt (WHO-III, n=118) patients was 23.7 (95% CI 16.8% to 32.9%) after 1 year and 43.0% (95% CI 34.1% to 53.2%) after 2 years. In contrast, the *TERT*-alt (WHO-III, n=22) patients had a cumulative incidence of recurrence with a 1-year and 2-year rate of 52.5% (95% CI 34.6% to 74.6%) and 70.4% (95% CI 50.1% to 87.8%), respectively (Gray's test p=0.01, figure 4B). In further comparison with *TERT*p-wt (WHO-III) patients, *TERT*-alt (WHO-I and WHO-II, n=37) patients had a significantly poorer prognosis: the 1 year cumulative incidence of recurrence was 35.1% (95% CI 22.1% to 52.7%) whereas the 2 years cumulative incidence of recurrence was 60.1% (95% CI 45.2% to 75.7%) (Gray's test p=0.002, figure 4C).

### Cox regression analysis

In the unadjusted model, women (n=369) had a lower risk of recurrence after the initial 36 months compared with men (n=298) with an HR of 0.50 (95% CI 0.33 to 0.75). We found that a 10-year increase in age at diagnosis increased the risk of recurrence with an HR of 1.14 (95% CI 1.04 to 1.25). As expected, the risk of recurrence increased gradually with higher WHO grade. With WHO-I meningiomas (n=169) as reference,

**Table 1A** Study characteristics

| | Goutagny *et al*[7] 2014, n=61 | Sahm *et al*[5] 2016, n=255 | Juratli *et al*[8] 2017, n=26 | Peyre *et al*[9] 2018, n=52 | Biczok *et al*[10] 2018, n=88 | Spiegl-Kreinecker *et al*[11] 2018, n=89 | Juratli *et al*[12] 2018, n=42 | Bertero *et al*[25] 2019, n=64 | |
|---|---|---|---|---|---|---|---|---|---|
| **Study design** | **Retrospective** | **Retrospective** | **Retrospective** | **Retrospective** | **Retrospective** | **Retrospective** | **Retrospective** | **Retrospective** | **All combined n=677** |
| *TERT* gene alterations | | | | | | | | | |
| C228A *or* C228T | 5 | NA | 3 | 8 | 2 | 6* | NA | 4 | 28 |
| C250T | 1 | NA | 3 | 1 | 4 | 1 | NA | 1 | 11 |
| *Sum of patients with a mutation* (*% in cohort*) | 6 (9.8) | 16 (6.3) | 6 (23.1) | 8 (15.4)† | 6 (6.8) | 7 (7.9) | 2 (4.8) | 5 (7.8) | 56 (8.3) |
| TERT promoter fusion | 0 | 0 | 1‡ | 0 | 0 | 0 | 2§ | 0 | 3 |
| Laboratory test | PCR amplification | Sanger/PCR | Sanger | PCR amplification | PCR amplification | PCR amplification | Sanger | Sanger | |
| For the entire cohort | | | | | | | | | |
| Age, mean (SD) | 49.7 years (17.0) | 56.8 years (14.2) | 55.7 years (16.6) | 61.5 years (13.9) | 62.7 years (15.0) | 60.4 years (14.7) | NA | 59.1 years (13.5) | 57.9 years (15.0) |
| Sex (female/male) | 34/27 | 163/92 | 12/14 | 25/27 | 38/50 | 51/38 | 18/24 | 32/32 | 373/304 (=1.23) |
| WHO-I | 15 | 119 | 3 | 9 | 0 | 23 | 0 | 0 | 169 |
| WHO-II | 38 | 88 | 13 | 14 | 73 | 54 | 29 | 56 | 365 |
| WHO-III | 8 | 48 | 10 | 29 | 15 | 12 | 13 | 8 | 143 |
| Recur/p-yrs (RR) | 23/319.2 (7.2) | 99/1458.3 (6.8) | 19/8.7 (219.2) | 46/164.0 (28.1) | 51/236.5 (21.6) | 17/547.0 (3.1) | 36/152.8 (23.6) | 22/166.8 (13.2) | 313/3053.2 (10.3) |
| Deaths/p-yrs (MR) | 10/382.3 (2.6) | 28/857.2 (3.3) | 14/16.5 (85.0) | 44/313.7 (14.0) | 25/294.2 (8.5) | 38/598.3 (6.4) | 13/330.8 (3.9) | 20/311.7 (6.4) | 192/3104.7 (6.2) |

*One case was C228A.
†One patient harboured both the TERTp-C228T and TERTp-C250T mutation.
‡LPCAT1-TERT fusion.
§RETREG1-TERT fusion.
MR, mortality rate per 100 person-yrs; p-yrs, total person-yrs; Recur, total recurrences; RR, recurrence rate per 100 person-yrs.

**Table 1B** Patient characteristics stratified on *TERT*-alt

| | TERT-alt (*n=59*) | TERTp-wt (*n=618*) |
|---|---|---|
| Age, mean (SD) | 60.8 years (12.5) | 57.7 years (15.2)* |
| Sex (female/male) | 25/34=0.74 | 319/240=1.29 |
| WHO-I | 8 | 161 |
| WHO-II | 29 | 336 |
| WHO-III | 22 | 121 |
| Recurrences/person-years | 49/101.9 | 264/2951.3 |
| Recurrence rate per 100 person-years | 48.1 (95% CI 35.6 to 63.6) | 8.9 (95% CI 7.9 to 10.1) |
| Median recurrence-free survival | 14.0 months (95% CI 10 to 24) | 101.9 months (95% CI 90 to 123) |
| Dead/person-years | 37/193.2 | 155/2911.5 |
| Mortality rate per 100 persons-years | 19.2 (95% CI 13.5 to 26.4) | 5.3 (95% CI 4.5 to 6.2) |
| Median overall survival rate | 58 months (95% CI 33 to 77) | 160 months (95% CI 131 to 336) |

*n=521, age at diagnosis could not be retrieved from one study (n=38).[12]
*TERT*-alt, *TERT* gene alterations; *TERT*p-wt, *TERT* promoter wild-type.

the HR was 1.60 (95% CI 1.15 to 2.22) and 2.38 (95% CI 1.67 to 3.39) for WHO-II (n=358) and WHO-III (n=140), respectively. The HR for *TERT*-alt (n=59) was 3.82 (95% CI 2.76 to 5.28) compared with *TERT*p-wt (n=608) (table 2).

In the adjusted model, there was no difference between sexes during the initial 36 months, but the HR was 0.43 (95% CI 0.28 to 0.67) for women from 36 months and onwards compared with men. A 10-year increase in age at diagnosis was found to increase the risk of recurrence with a HR 1.10 (95% CI 1.00 to 1.20). WHO-II and WHO-III meningiomas had an HR of 1.38 (95% CI 0.98 to 1.93) and 2.27 (95% CI 1.58 to 3.25) compared with WHO-I, respectively. The HR for *TERT*-alt was 3.74 (95% CI 2.65 to 5.30) with *TERT*p-wt as reference group (table 2).

## Overall survival

The mortality rate was 3.6 (95% CI 2.5 to 5.2) times higher in *TERT*-alt (n=49) patients compared with *TERT*p-wt (n=478) patients (figure 2). *TERT*-alt (all) patients had a median survival of 58 months (95% CI 33 to 77) compared with 160 months (95% CI 131 to 336) in *TERT*p-wt (all) patients (log-rank test p<0.0001, figure 5A and table 1B). Moreover, *TERT*-alt (WHO-III, n=16) patients had a 6.8 (95% CI 4.1 to 11.4) times higher mortality rate than *TERT*p-wt (WHO-III, n=113) patients (figure 2). Similarly, a log-rank test indicated a significant difference in survival probability (p=0.0015) (figure 5B): the median survival was 25 months (95% CI 13 to not reached) and 79 months (95% CI 61 to not reached) in *TERT*-alt (WHO-III) patients and in *TERT*p-wt (WHO-III) patients, respectively. Similar trends were observed when evaluating *TERT*-alt (WHO-I and WHO-II, n=33) patients versus *TERT*p-wt (WHO-III) patients. The mortality rate was 2.7 times higher (95% CI 1.8 to 4.1) in *TERT*-alt (WHO-I and WHO-II) patients compared with *TERT*p-wt (WHO-III) patients. The median survival of *TERT*-alt (WHO-I and WHO-II) patients was 72 months (95% CI 54 to 113) and, as mentioned, 79 months (95% CI 61 to not reached) for *TERT*p-wt (WHO III) patients (log-rank test p=0.05, figure 5C).

From the likelihood ratio test, we found that the effect of *TERT*-alt on overall survival was not modified by sex ($\chi^2$ p=0.9) or WHO grade ($\chi^2$ p=0.2). However, for age at diagnosis, we found a significant effect modification ($\chi^2$ p=0.04). The effect of *TERT* on age at diagnosis was more profound in younger patients compared with older patients.

## Cox regression analysis

In the unadjusted model, women (n=270) and men (n=257) had a higher risk of death the initial 36 months with an HR of 2.90 (95% CI 1.86 to 4.54). However, women had a lower risk of death after the initial 36 months with an HR of 0.64 (95% CI 0.44 to 0.93) (table 2). A 10-year increase in age at diagnosis increased the risk of death with an HR of 1.61 (95% CI 1.41 to 1.83). As expected, increasing WHO grades were gradually associated with a higher HR. With WHO-I meningiomas (n=78) as reference, the HR was 1.89 (95% CI 1.17 to 3.05) and 3.61 (95% CI 2.21 to 5.91) for WHO-II (n=320) and WHO-III (n=129), respectively. *TERT*-alt (n=49) had an HR of 2.84 (95% CI 1.96 to 4.13) with *TERT*p-wt (n=478) as reference (table 2).

In the adjusted model, women had a higher risk of death the initial 36 months with an HR of 2.86 (95% CI 1.80 to 4.54); however, women had a lower risk of death after the initial 36 months with an HR of 0.56 (95% CI 0.39 to 0.82). A 10-year increase in age at diagnosis was associated to death with an HR 1.52 (95% CI 1.33 to 1.74). The HR increased for increasing WHO grades: WHO-II and WHO-III meningiomas had an HR of 1.45 (95% CI 0.89 to 2.37) and 2.65 (95% CI 1.60 to 4.39) compared with WHO-I, respectively. *TERT*-alt had an HR of 2.77 (95% CI 1.86 to 4.11) with *TERT*p-wt as reference (table 2).

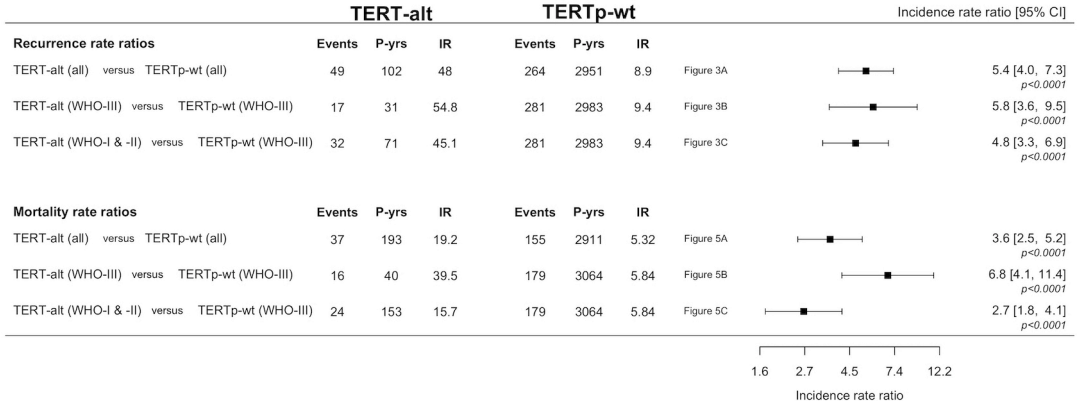


**Figure 2** Incidence rates (events/100 person-years) and rate ratios for recurrence and death for different subgroups of *TERT* gene alterations (*TERT*-alt) and *TERT* promotor wild-type (*TERT*p-wt). IR, incidence rate per 100 persons-years; P-yrs, person-years.

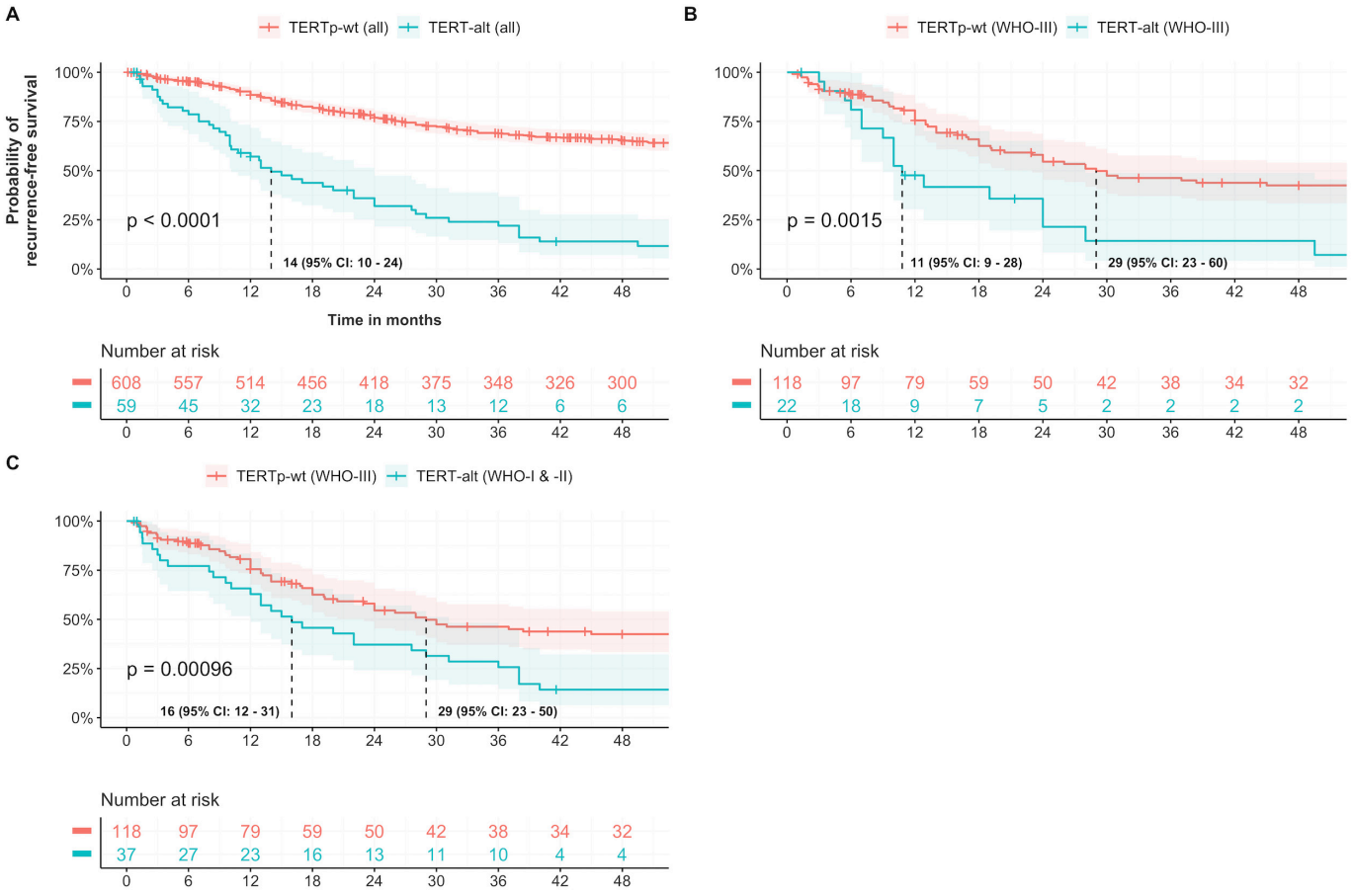


**Figure 3** (A) Recurrence-free survival of all grades *TERT*p-wt (all) versus all grades *TERT*-alt (all). (B) Recurrence-free survival of WHO-III: *TERT*p-wt (WHO-III) versus all grades *TERT*-alt (WHO-III). (C) Recurrence-free survival of WHO-III wild-type, *TERT*p-wt (WHO-III) versus WHO-I and WHO-II combined of *TERT*-alt, *TERT*-alt (WHO-I and WHO-II). *TERT*-alt, *TERT* gene alterations; *TERT*p-wt, *TERT* promotor wild-type.

## DISCUSSION

Here, we present a meta-analysis of individual meningioma patient data harbouring *TERT*-alt. To our knowledge, our meta-analysis includes the largest number of meningioma patients with *TERT* alterations published to date. This include all published cases with analyses of recurrence-free and overall survival until 25 June 2019. Our meta-analysis confirms previous findings that *TERT*-alt meningioma patients had significantly higher risk of recurrence than *TERT*p-wt patients. Furthermore, we have evidently confirmed that *TERT*-alt patients also render a poorer overall survival compared with *TERT*p-wt meningioma patients.

We show that *TERT*-alt (WHO-III) patients and even *TERT*-alt (WHO-I and WHO-II) patients had a significantly higher recurrence rate as well as higher mortality rate than *TERT*p-wt (WHO-III) patients. We saw an increased risk of recurrence and death in the *TERT*-alt meningioma group, compared with their *TERT*p-wt counterpart in the adjusted Cox regression analysis that included multiple factors (age at diagnosis, sex, WHO grade and centre effect).

We detected differences in the clinical characteristics of *TERT*-alt patients when compared with their *TERT*p-wt counterparts. Namely, male patients were over-represented among *TERT*-alt patients, and *TERT*-alt patients were slightly older than *TERT*p-wt patients. Notably, *TERT*-alt occurred in meningioma of all WHO grades; however, the effect of *TERT*-alt on the recurrence and mortality rate was not modified by WHO grade. Thus, the poor prognosis associated with *TERT*-alt was independent of WHO grade.

Most importantly, our findings highlight the incongruence that is implied within the current WHO classification for meningioma and evidently demonstrate the dismal prognosis associated with acquiring *TERT*-alt in meningioma.

The WHO classification describes 15 different histological subtypes and does not, however, use molecular markers. The grading is based on visual assessment of histology that includes an element of subjectivity and is prone to interobserver bias.[6] Furthermore, the WHO grading does not correlate with clinical course in all cases. While WHO grade I meningiomas are considered benign with few cases that have aggressive phenotypes, a substantial fraction of WHO grade II and WHO grade III meningiomas tumours have a less favourable natural history.[35–37]

Molecular profiling has been introduced to improve WHO classification for other CNS tumours. For instance, distinct epigenetic subgroups of medulloblastoma[38–40] as well as isocitrate dehydrogenase 1/2 status and 1p/19q status in diffuse gliomas provide prognostic information that can serve to tailor management of the patient.[41–43]

Molecular data that correlates with clinical phenotypes is becoming available for meningiomas.[44 45] Sahm *et al*,[45] as an example, generated genome-wide methylation profiles, which revealed two major epigenetic groups: group A and group B. Group A comprises four subgroups, three benign and one intermediate, whereas group B comprises two subgroups, one intermediate and one malignant. Interestingly, the methylation-based classification showed a better correlation with the clinical behaviour than the WHO classification. Notably, four of the

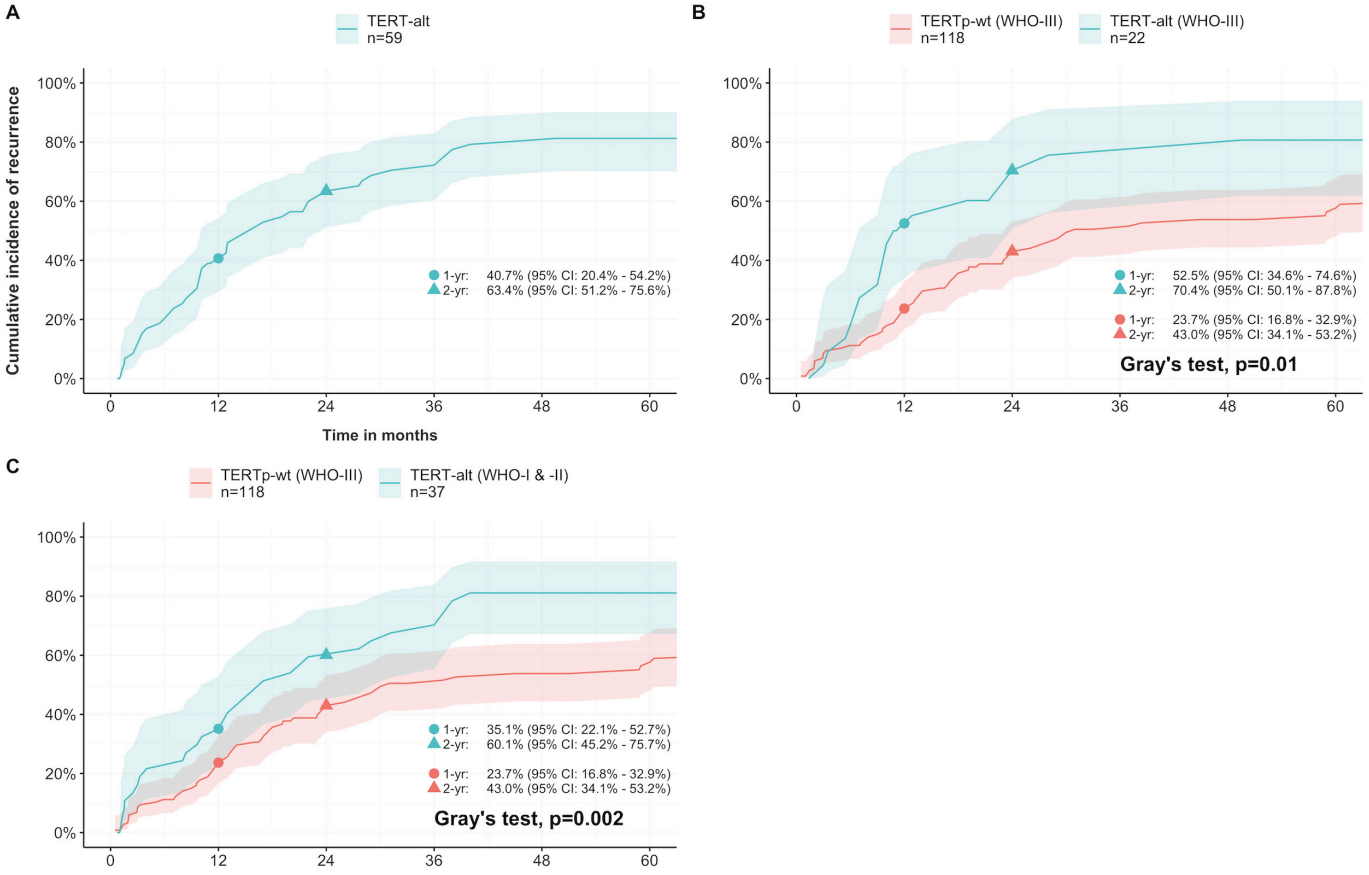


**Figure 4** (A) Cumulative incidence of recurrence in *TERT*-alt, when considering death *without* recurrence as competing risk. (B) Cumulative incidence of recurrence in *TERT*p-wt (WHO-III) versus *TERT*-alt (WHO-III) when considering death *without* recurrence as competing risk. (C) Cumulative incidence of recurrence in *TERT*p-wt (WHO-III) versus *TERT*-alt (WHO-I and WHO-II) when considering death *without* recurrence as a competing risk. *TERT*-alt, *TERT* gene alterations; *TERT*p-wt, *TERT* promoter wild-type.

five meningiomas with *TERT*-alt in their cohort were mapped to group B.[45]

## Strengths and limitations

The major strength of this IPD meta-analysis is the inclusion rate of 100% of all published articles on *TERT* gene alterations in meningioma. The strength of IPD meta-analyses is the simultaneous analysis of raw data from included studies, which allows for a better statistical adjustment and exploration of data compared with traditional meta-analyses of aggregated data.

However, our meta-analysis had some limitations. It was not possible to include or adjust for the extent of surgical resection, which is recognised as prognostically important.[46–49] Moreover, it was not known whether the included patients received other

**Table 2** HRs and 95% CIs from Cox regression models

| | Recurrence | | Death | |
|---|---|---|---|---|
| | Unadjusted HR (95% CI) | Adjusted HR (95% CI) | Unadjusted HR (95% CI) | Adjusted HR (95% CI) |
| Male (≤36 months) | Ref. | Ref. | Ref. | Ref. |
| Female (≤36 months) | 0.83 (0.63 to 1.09) | 0.90 (0.67 to 1.19) | 2.90 (1.86 to 4.54) | 2.86 (1.80 to 4.54) |
| Male (>36 months) | Ref. | Ref. | Ref. | Ref. |
| Female (>36 months) | 0.50 (0.33 to 0.75) | 0.43 (0.28 to 0.67) | 0.64 (0.44 to 0.93) | 0.56 (0.39 to 0.82) |
| Age at diagnosis, per 1-year increase | 1.01 (1.00 to 1.02) | 1.01 (1.00 to 1.02) | 1.05 (1.04 to 1.06) | 1.04 (1.03 to 1.06) |
| Age at diagnosis, per 10-year increase | 1.14 (1.04 to 1.25) | 1.10 (1.00 to 1.20) | 1.61 (1.41 to 1.83) | 1.52 (1.33 to 1.74) |
| WHO-I | Ref. | Ref. | Ref. | Ref. |
| WHO-II | 1.60 (1.15 to 2.22) | 1.38 (0.98 to 1.93) | 1.89 (1.17 to 3.05) | 1.45 (0.89 to 2.37) |
| WHO-III | 2.38 (1.67 to 3.39) | 2.27 (1.58 to 3.25) | 3.61 (2.21 to 5.91) | 2.65 (1.60 to 4.39) |
| *TERT*p-wt | Ref. | Ref. | Ref. | Ref. |
| *TERT*-alt | 3.82 (2.76 to 5.28) | 3.74 (2.65 to 5.30) | 2.84 (1.96 to 4.13) | 2.77 (1.86 to 4.11) |

The unadjusted estimates were adjusted to centre effect, exclusively. The adjusted models included centre effect, WHO age at diagnosis, sex and *TERT*-alt. Sex was evaluated in the two different time periods to accommodate the assumption of proportionality: first, from 0 to 36 months; and second, after 36 months.
NA, not applicable; *TERT*-alt, *TERT* gene alterations.

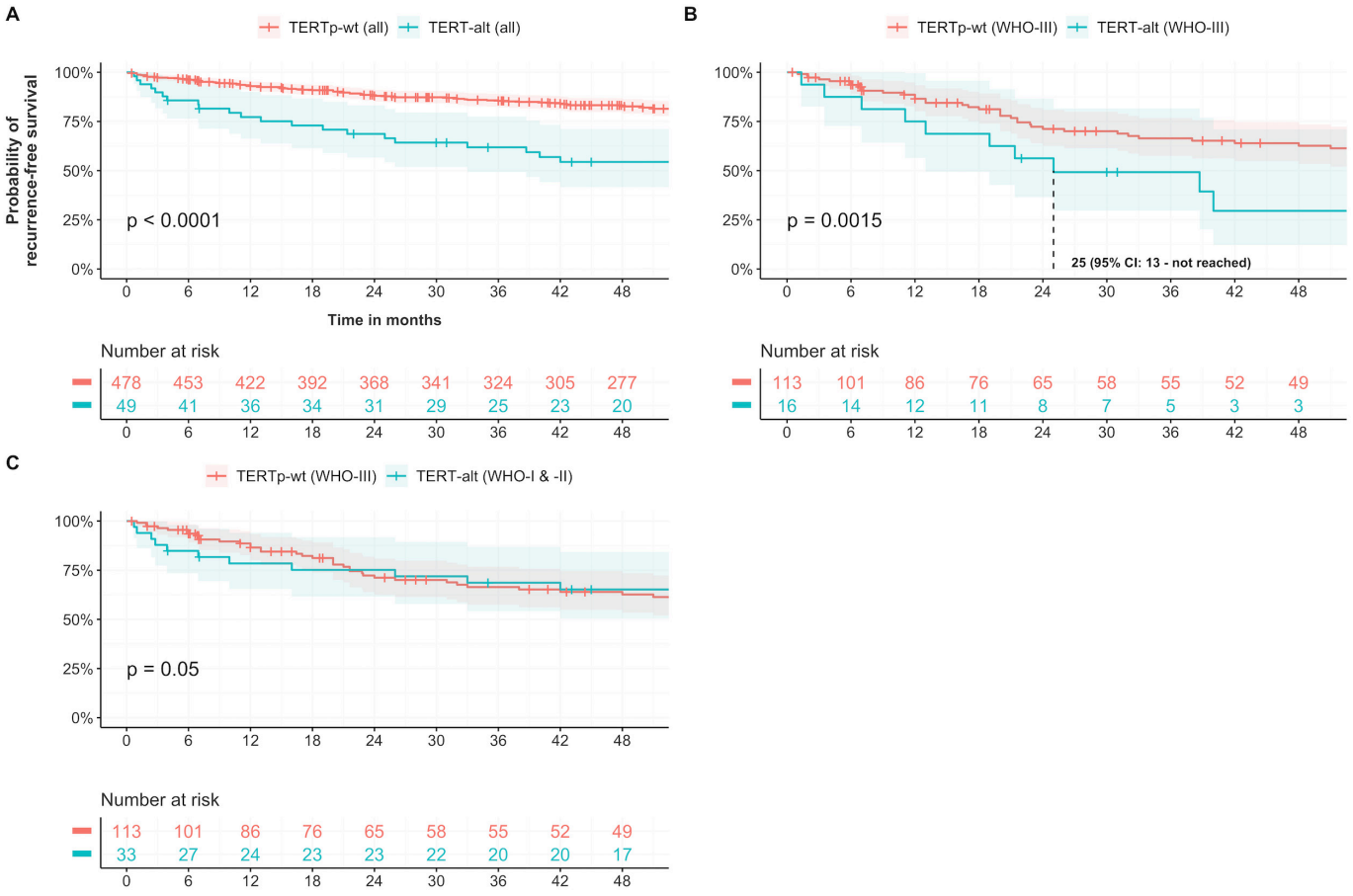


**Figure 5** (A) Overall survival of all grades *TERT*p-wt (all) versus all grades *TERT*-alt (all). (B) Overall survival of WHO-III: *TERT*p-wt (WHO-III) versus all grades *TERT*-alt (WHO-III). (C) Overall survival of WHO-III wild-type, *TERT*p-wt (WHO-III), versus WHO-I and WHO-II combined of *TERT*-alt, *TERT*-alt (WHO-I and WHO-II). *TERT*-alt, *TERT* gene alterations;*TERT*p-wt, *TERT* promoter wild-type.

treatment than surgery that might have affected the prognosis. In addition, we only had limited access to information whether the included high-grade meningiomas were de novo or secondary, which also may affect prognosis.[7 9] Furthermore, the majority of patients in the included studies has been classified according to WHO 2007 and not the WHO 2016 classification.[3] However, evidence of microscopic brain invasion (as stand-alone grading criterion for atypical meningiomas) was the only change, which would not be expected to impact the presented results in this study. It was not possible to adjust for important comorbidities, such as other cancer diagnoses, cardiovascular disease and other major risk factors that might affect the prognosis. Finally, the patients included in each individual study were highly selected and not consecutive. Hence, the incidence and prevalence of *TERT*-alt in meningioma remain unestablished. However, our research objective was to investigate the effect of *TERT*-alt independently of the WHO classification and was not limited by the selection process applied within the included studies. Thus, we do not consider selection bias a relevant parameter for this study.

## Comparison with literature

Notwithstanding, we acknowledge that the population in our IPD meta-analysis differed from what would be expected from a large meningioma cohort. Our sex ratio for females to males was 5:4, which was in alignment with higher incidences of meningioma in women, but lower than the 2:1 distribution in population-based epidemiological reports.[22 50] However, the higher proportion of males might be explained by the high number of WHO-II and WHO-III meningioma aggregated in this study, which have higher male frequency.[51 52] Given that we are searching for biomarkers of aggressive behaviour, a skewed population with more aggressive phenotypes would not affect the external validity.

Noteworthy, a meta-analysis of published data on *TERT* promoter mutations was previously published in December 2018.[53] However, that study had not accessed and analysed original data as was done in this study and included fewer studies.

## Clinical implications

Our analysis confirmed that *TERT*-alt is a reliable prognostic biomarker in meningioma which, when present, rendered a remarkable poorer outcome independent of WHO grade.

The incidence of *TERT*-alt has not been established in consecutively collected meningiomas, but our analysis supports the generally reported rate of 6%–8% in all meningiomas. Given that meningiomas are the most common intracranial neoplasm, a large patient cohort may be affected by *TERT*-alt. *TERT*-alt is an important and reliable prognostic biomarker. Independent of WHO grade, we found that *TERT*-alt patients did consistently worse compared with *TERT*p-wt patients—even *TERT*-alt (WHO-I and WHO-II) rendered a poorer recurrence-free and overall survival compared with *TERT*p-wt (WHO-III) patients. Hence, WHO-I and WHO-II patients with *TERT*-alt might be allocated to treatment and follow-up algorithms that is not currently balanced by the aggressive behaviour in this meningioma genotype. The prognosis of these patients may be

improved by more aggressive treatment management and planning. We therefore propose that (1) analysis of *TERT*-alt should be integrated as a standard laboratory test in the histopathological diagnosis of meningiomas and (2) that should be implemented into the WHO classification of meningioma.

Specifically, one might consider whether a fourth WHO grade of malignancy should be introduced to accommodate the most aggressive genotypes, and it is possible that *TERT*-alt could define such a group of meningiomas. Based on the presented findings, lack of TERT promoter mutation detection in progressive/high-grade meningioma may not be sufficient to classify a meningioma as TERT wild type, and additional molecular evaluation for TERT gene rearrangements should be considered in such cases.[23]

Regardless of changes in classification, our findings have a clear impact on management of patients with *TERT*-alt meningiomas: *TERT*-alt patients should be managed and surveilled aggressively. Prospective trials to determine if *TERT*-alt should be treated independently of the WHO grade and equally to WHO-III are warranted. As for now, we suggest that WHO-I and WHO-II meningiomas with confirmed *TERT*-alt should be allocated to the same observational algorithm as WHO-III.

## CONCLUSIONS

Our meta-analysis analysed original data from 677 patients provided by the authors of all hitherto published studies on *TERT*-alt in meningiomas.

*TERT*-alt occur in all WHO grades of meningioma. The effect of *TERT*-alt was not modified by WHO grade. This study indicates that *TERT*-alt is a biomarker yielding significantly higher recurrence and mortality rate in meningiomas. This is an important finding, given that meningiomas are the most common intracranial neoplasms. Thus, *TERT*-alt potentially affect a large population in which prognosis can be improved by better treatment management and planning.

Prospective trials should determine the ideal management of *TERT*-alt patients. Awaiting these, *TERT*-alt patients should probably be managed aggressively regarding surgical planning, radiotherapy and follow-up independent of WHO grade. This include that *TERT*-alt in WHO-I and WHO-II meningiomas should be allocated to the same treatment algorithm as WHO-III. We propose that *TERT*-alt detection should be implemented as a routine diagnostic test in meningioma and integrated into the next WHO classification. However, it is still premature to implement an additional WHO grade, WHO-IV, for meningiomas based on the presented results.

**Author affiliations**
[1]Department of Neurosurgery, Copenhagen, Copenhagen University Hospital, Denmark
[2]Danish Cancer Society Research Center, Statistics and Pharmacoepidemiology, Copenhagen, Denmark
[3]Department of Neurosurgery, Translational Neuro-Oncology Laboratory, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, United States
[4]Department of Neurosurgery, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
[5]German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany
[6]Department of Neuropathology, Institute of Pathology, Heidelberg University Hospital, Heidelberg, Germany
[7]Department of Neurosurgery, Kepler University Hospital GmbH, Johannes Kepler University, Linz, Austria
[8]Department of Neurosurgery, Sorbonne Université, Groupe Hospitalier Pitié-Salpêtrière, Paris, France
[9]Department of Neurosurgery, Ludwig-Maximilians-University Munich, Munich, Germany
[10]Department of Neurosurgery, Assistance Publique-Hôpitaux de Paris, Hôpital Beaujon, Clichy, Paris, France
[11]Department of Medical Sciences, Pathology Unit, University of Turin, Torino, Italy
[12]Department of Clinical Physiology, Nuclear Medicine and PET, Copenhagen University Hospital, Copenhagen, Denmark
[13]Department of Neuropathology, Center of Diagnostic Investigation, Copenhagen University Hospital, Copenhagen, Denmark
[14]Department of Medicine, Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA
[15]Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark
[16]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[17]Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden

**Contributors** Study design, idea and writing: CM (lead writer), ADM, MMP, IL, HB, LP, KF, MZ, TinM and TiiM. Statistics and methods: CM, AKD-H (certified statistician) and TinM (epidemiologist). Producing data and patient follow-up: TJ, FS, SS-K, MP, AB, J-CT, SG, LB, DPC and PB. Editing and formatting the manuscript: all.

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**ORCID iD**
Christian Mirian http://orcid.org/0000-0001-6801-0123

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