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Impact of *TERT* and *CDKN2A/B* driver mutations on meningioma recurrence: a systematic review and meta-analysis

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ABSTRACT

Background. Evolution of the WHO classification for meningiomas demonstrates a shift towards integrative approach, where molecular markers are essential for risk stratification. However, their prognostic significance depending on histological grade requires further clarification.

Objective. To evaluate the impact of *TERT* promoter mutations and *CDKN2A/B* deletions on meningioma recurrence, stratified by tumor grade.

Material and methods. A systematic review and meta-analysis (PRISMA-P) of 17 cohort studies (*n*=5867) was conducted. Random-effect models and network meta-analysis were employed to assess overall survival (OS) and progression-free survival (PFS).

Results. The *TERT* mutation significantly worsens prognosis (OS HR=2.78; PFS HR=2.63), but the effect is context-dependent. In WHO Grade 1–2 tumors, it acts as a potent driver of aggression (HR~5.00, "initiation effect"), whereas in Grade 3 its contribution diminishes (HR~1.5) amidst general genomic instability. Homozygous deletion of *CDKN2A/B* is confirmed as a universal marker of early recurrence (HR=3.72) with up to 5-fold risk increment. Sensitivity analysis revealed that clonal mutations (detected by Sanger sequencing) hold greater prognostic value than subclonal ones (detected by NGS).

Conclusion. *TERT* screening is essential for WHO Grade 1 and 2 meningiomas to identify occult aggression, while *CDKN2A/B* assessment is a priority for Grade 3 tumors.

Keywords: *meningioma recurrence, TERT promoter mutation, CDKN2A/B homozygous deletion, driver mutations.*

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Introduction

Evolution of the WHO classification of meningiomas demonstrates a shift from morphological assessment to integrative approach. While early editions (1979—2016) relied on histological criteria and a 3-grade system, the 5th edition (2021) introduced molecular markers. Currently, CDKN2A/B deletion or TERT mutation automatically establish meningioma WHO grade III [1]. Clinical experience demonstrated significant limitations in a purely morphological system. First, reproducibility of histological assessment is constrained by persistent high inter-observer variability. Diagnostic concordance is the lowest when verifying WHO grade II status and assessing brain tissue invasion. This fre-

quently leads to diagnostic discrepancies and complicates selection of adjuvant therapy [2]. Second, there are prognostic inconsistencies. Indeed, some WHO grade I meningiomas recur and demonstrate aggressive behavior, whereas certain WHO grade II tumors possess a "benign" molecular profile and remain clinically indolent [4].

Molecular-genetic patterns of meningiomas reveal a distinct genetic dichotomy closely associated with tumor location, morphology and prognostic profile.

The first relatively benign lineage comprises chromosomally stable skull base meningiomas harboring mutations in TRAF7, KLF4, AKT1, SMO and PIK3CA. TRAF7 comutations with KLF4 or AKT1 are associated with WHO grade I status and favorable outcomes, whereas SMO mutations may carry higher risk of recurrence [5].

The second group (predominantly convexital and parasagittal tumors) is characterized by chromosomal instability, NF2 inactivation and 1p/14q/22q deletions following a model of clonal evolution. Although the 2021 WHO classification formally equates TERT mutations and CDKN2A/B deletions as markers of WHO grade III status, CDKN2A/B deletion demonstrates a higher risk of progression (hazard ratio [HR] 8.4; 5-year recurrence-free survival 11.1%). Even heterozygous deletion exerts a significant impact (HR=5.5), necessitating refinement of risk hierarchy [6].

Widespread clinical implementation of molecular-morphological classification is limited by necessary standardization, high costs and insufficient availability of specialized platforms for methylation analysis [7].

We prepared a systematic review and meta-analysis based on previous protocol [8]. Meta-analysis aims to examine concomitant influence of three key factors on tumor recurrence: extent of resection, tumor grade, and genetic profile. The latter factor could significantly modify treatment approaches and determine mutational composition of standardized genetic diagnostic panel.

Material and methods

Meta-analysis of prognostic factors for meningioma recurrence was based on the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2020 guidelines. Screening of the PubMed, Web of Science, eLibrary, Scopus and Google Scholar databases (Publish or Perish software) using appropriate keywords ("meningioma", "genetic markers" (CDKN2A, TERT, NF2), and "recurrence") identified 1.138 unique abstracts (deduplication in Zotero software). Two specialists selected articles in two stages: screening of titles / abstracts to identify cohort and randomized controlled stud-

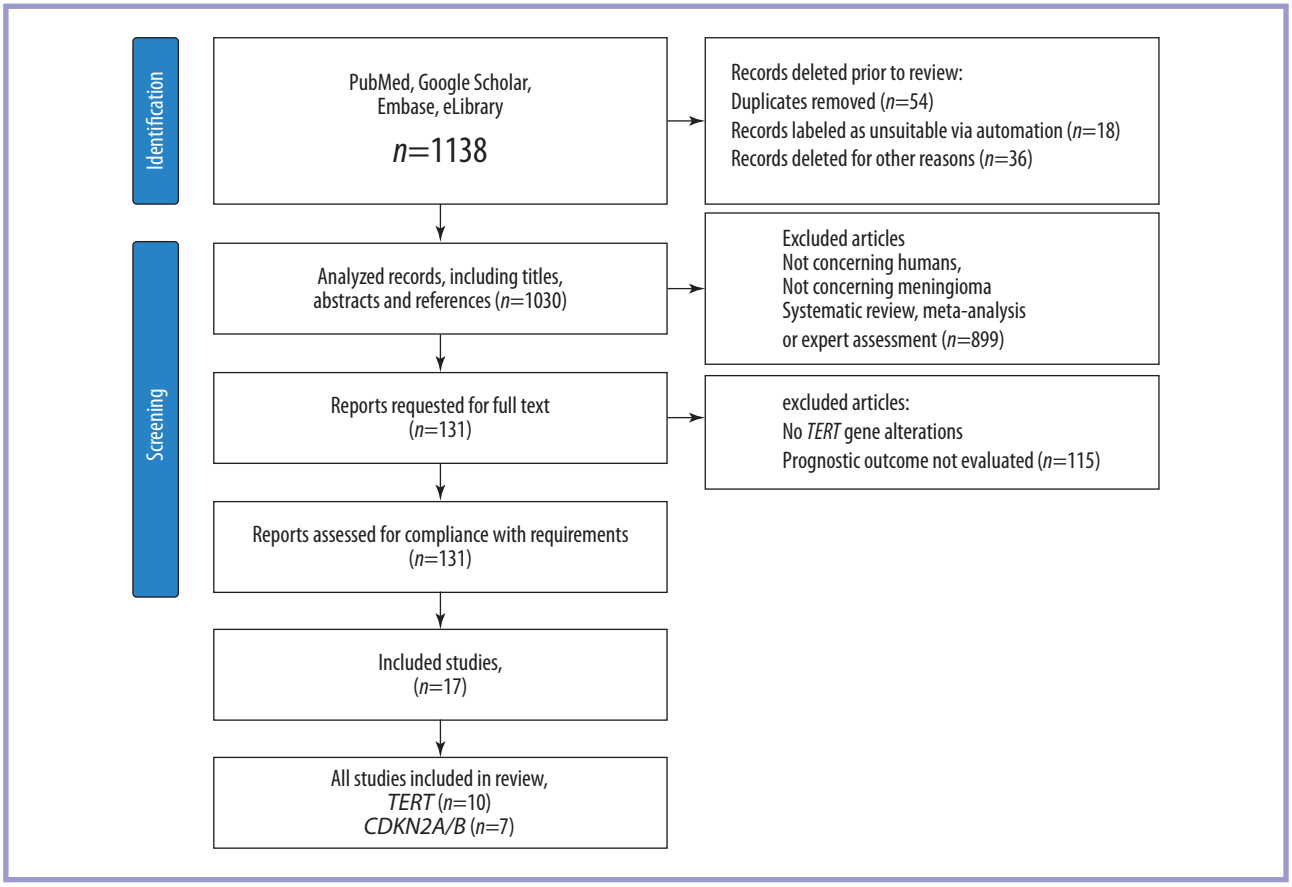

Fig. 1. **Study flowchart (PRISMA-P).**

ies followed by assessment of 131 full-text articles for compliance with PICOTS criteria (Population, Intervention, Comparison, Outcome, Timing, Setting) **(Table 1)**. Disagreements were resolved through consensus. Final analysis enrolled 17 articles (10 regarding TERT mutations and 7 regarding CDKN2A/B) **(Fig. 1)**.

Impact of TERT mutations on the risk of meningioma recurrence was described in 10 retrospective cohort studies published between 2014 and 2024 **(Table 2)** [1—18]. Total sample comprised 2.392 patients. Study design ranged from large multiple-center studies (Groff K.J. et al., *n*=1545; Sahm F. et al., *n*=252) to single-center cohorts focused on aggressive phenotypes (Juratli T.A. et al., Peyre M. et al.) [1, 10, 14, 16].

Meta-analysis regarding the impact of CDKN2A/B included 7 retrospective cohort studies published between 2020 and 2024 (3.475 patients with various meningiomas) **(Table 3)** [19—25]. Study design ranged from small-scale single-center series focusing on aggressive subtypes (Barresi V. et al., *n*=22; Tosefsky K. et al., *n*=15; Sasaki S. et al., *n*=30) to large-scale, multiple-center studies using omics technologies (Wang J.Z. et al., *n*=1.577; Khan A.B. et al., *n*=776) [20—22, 24, 25].

Demographic data and extent of resections are presented in **Table 4**, 5.

Assessment of bias

We assessed risk of bias in observational studies using the QUIPS (Quality in Prognostic Studies) tool and considered critical confounders (TERT and CDKN2A/B mutations, malignancy grade). Among 10 studies, Groff K.J. et al. presented the most significant results, whereas Goutagny S. et al., Juratli T.A. et al. (2017) and Deng J. et al. demonstrated high risk of selection bias with necessary sensitivity analysis [1, 15, 17, 18]. In a subgroup of 7 articles (CDKN2A/B analysis), studies with small sample sizes (Barresi V. et al., Tosefsky K. et al.) were characterized by high risk of bias in contrast to representative series Wang (J.Z. et al., Khan A.B. et al., Driver J. et al.) [20—24]. High validity of methods (fluorescence in situ hybridization, next-generation sequencing) and data availability (HR and 95% CI in 6 out of 7 studies) together with contribution of large-scale studies ensure significance of results **(Fig. 2a**, b).

To assess the impact of TERT promoter and CDKN2A/B mutations on overall and disease-free survival, we used the inverse-variance method and the DerSimonian—Laird random-effect model due to heterogeneous study designs and population characteristics.

We evaluated causes of heterogeneity via univariable meta-regression of log(HR) (WLS, random-effect model) and estimated proportion of explained variance (relative reduction in τ^2) for two covariates: tumor grade (I—II vs. III) and adjustment for CDKN2A/B status and extent of resection.

A pooled analysis of 9 cohorts demonstrates that TERT promoter mutation is associated with significantly worse prognosis. The pooled hazard ratio (pHR) was 2.78 (95% CI: 1.44—5.39; $p<0.001$) for overall survival and 2.63 (95% CI: 1.58—4.38; $p<0.001$) for disease-free survival **(Fig. 3)**.

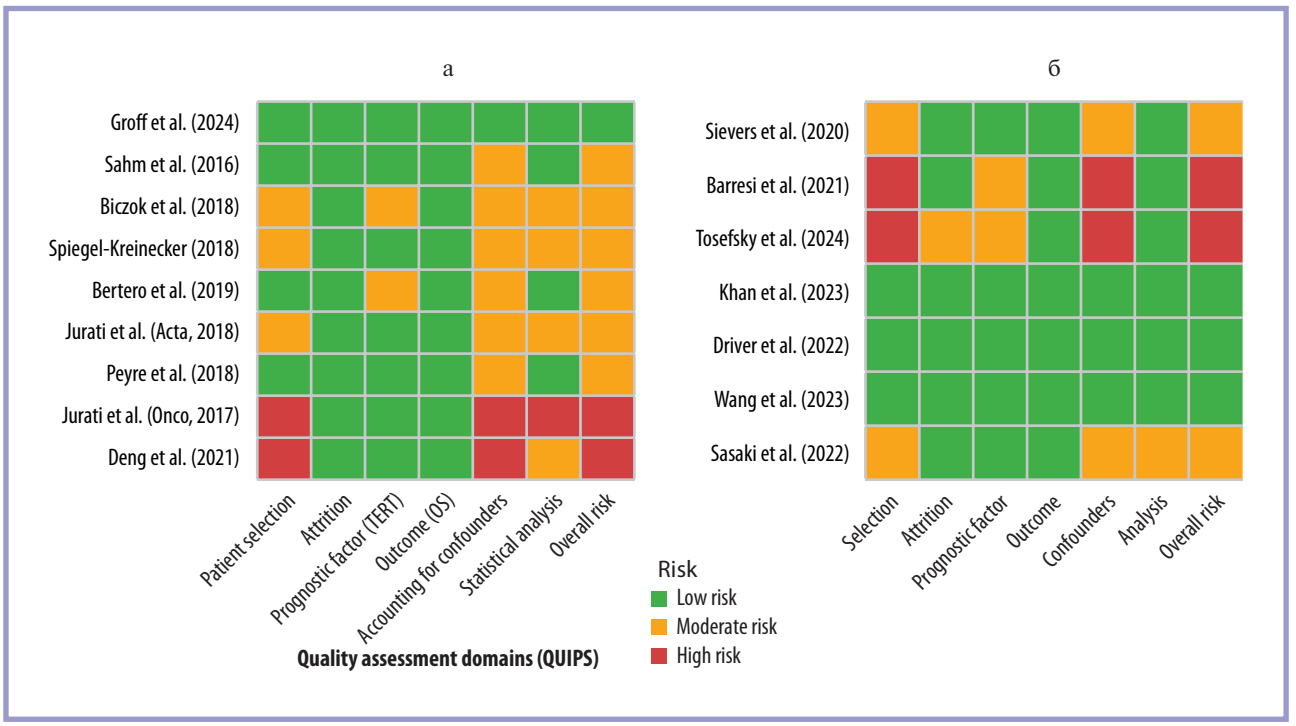

Fig. 2. **Risk of bias by domain for articles concerning TERT (a) and CDKN2A/B (b).**

However, we found significant heterogeneity across studies: high index for overall survival (I^2=78.3%; Q=36.86, df=8, p<0.001) and moderate one for disease-free survival (I^2=55.6%; Q=11.27, df=5, p=0.046). Thus, variability in results is due to not only random sampling error but also systematic differences between studies.

Pooling data from four articles established that homozygous CDKN2A/B deletion was a strong independent predictor of early recurrence (pHR 3.72, 95% CI: 2.08—6.65; p<0.001 for disease-free survival). Heterogeneity assessment revealed substantial inconsistency in results across studies (I^2=59.7%; Q=7.44, df=3, p=0.053). However, direction of effect was consistent across all studies (HR >1) and confirmed robustness of association.

Sources of heterogeneity and sensitivity

Leave-one-out sensitivity analysis enabled decomposition of heterogeneity in results [1] **(Fig. 1)**. Among studies devoted to TERT, excluding the study by Groff et al. (2024) as the largest sample size (n=1.545) and the only one adjusting for CDKN2A/B status substantially increased pHR for overall survival from 2.78 to 3.43 (95%

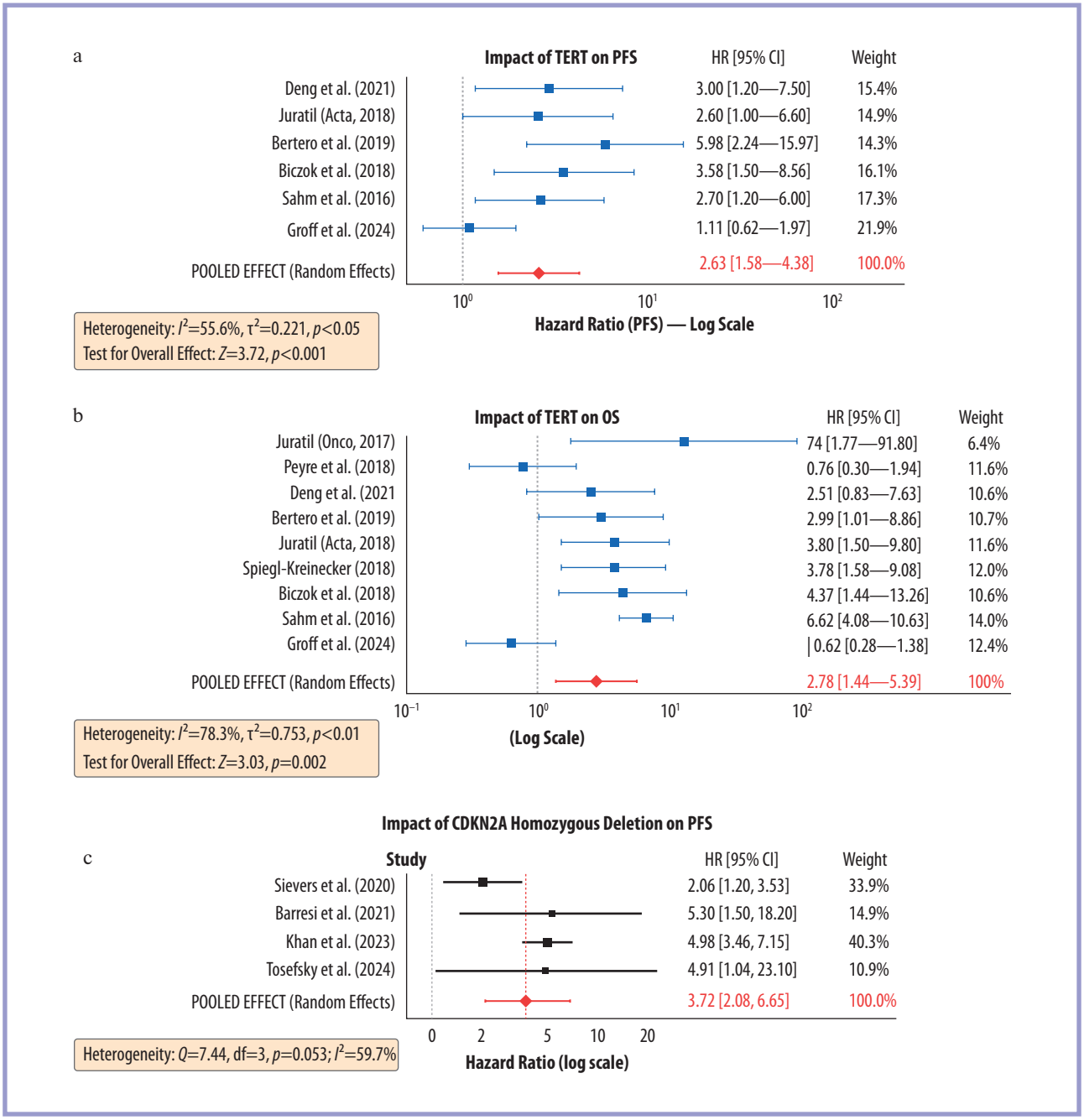

Fig. 3. **Overall effect of TERT (a, b) and CDKN2A/B (c) on overall and disease-free survival.**

CI: 1.97—5.96). Heterogeneity (I^2) decreased from 78.3% to 62.6%, and residual variability was due to the study by Peyre et al. enrolling exclusively anaplastic meningiomas. A similar trend was observed for disease-free survival. Excluding the study by Groff et al. increased HR from 2.63 to 3.32 while completely eliminating heterogeneity (I^2=0) **(Fig. 4)** [1, 16].

In the CDKN2A/B group, analysis confirmed significant association with disease-free survival: exclusion of any study did not affect significance of result (HR 3.25—4.97). The study by Sievers P. et al. [19] was the primary cause of variability. Its exclusion reduced I^2 from 59.5% to 0% while increasing pHR to 5.00 (95% CI: 3.56—7.02). That study yielded the most conservative risk estimate, likely due to effect dilution within a large cohort. In contrast, high consistency among studies of aggressive phenotypes confirms a fivefold increase in recurrence risk (HR ~5.0) in the presence of deletion [20—22]. This recognizes CDKN2A/B as a marker of "molecular anaplasia" classifying meningioma as highest-risk regardless of histological grade.

Subgroup analysis

Subgroup analysis included articles devoted to TERT, since CDKN2A/B subgroup did not require this analysis due to high consistency of data in sensitivity analysis. This analysis proposes a model of context-dependent prognostic value with direct clinical implications.

The TERT mutation is an independent and potent driver of aggressive behavior for grade I and II tumors (initiation effect), where the frequency of spontaneous CDKN2A/B deletions is low (HR=5.00, I^2=0%). Clinically, this implies that detection of TERT alterations in meningioma otherwise expected to follow indolent course should be regarded as a high-risk marker (equivalent to higher malignancy grade) and war-

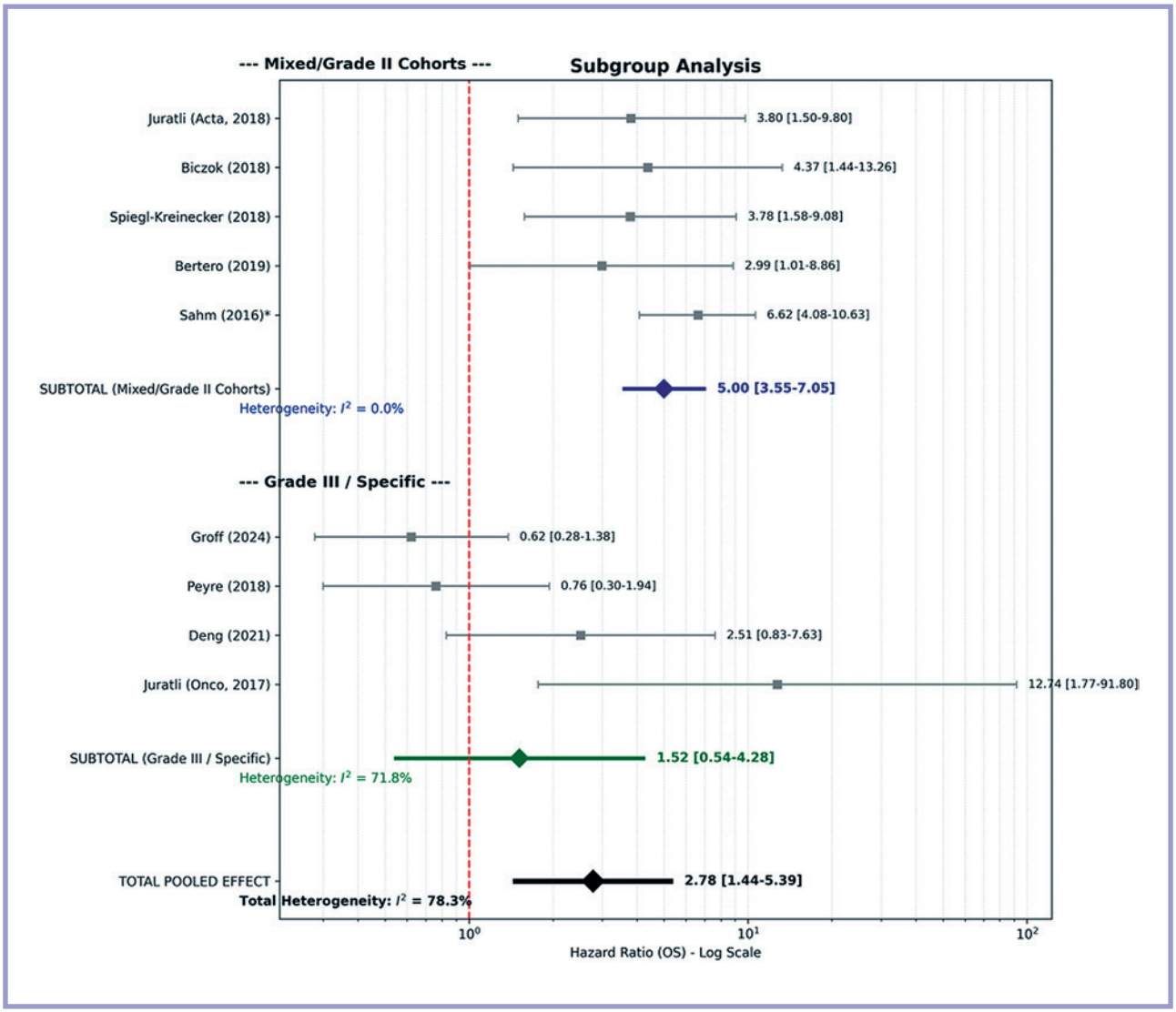

Fig. 4. **Context-dependent influence of TERT on prognosis.**

rants more aggressive management (e.g., early adjuvant therapy). Prognostic curve reaches a plateau (saturation effect) for grade III tumors. Additional prognostic contribution of TERT becomes minimal under genomic instability and frequent losses of 1p/14q and CDKN2A/B (HR=1.5). Consequently, TERT testing in patients with grade III tumor is less informative than CDKN2A/B analysis **(Fig. 4)**.

Impact of assay sensitivity

Meta-analysis data indirectly support the hypothesis regarding the role of clonality. Higher risk estimates observed in studies with Sanger sequencing are likely attributable to detection of exclusively clonal mutations present in majority of tumor cells. In contrast, highly sensitive methods (NGS) detect minor subclones, which may not exert such a detrimental impact on disease outcome [10, 11]. This underscores the need to standardize testing methods and allelic burden thresholds in clinical guidelines.

Meta-regression

Categorical meta-regression (WLS, random-effect model; 9 studies of overall survival) confirmed the hypothesis about context-dependent effect of TERT alterations. Tumor grade (I—II vs. III) was a significant moderator (β=−1.24; SE 0.46; p=0.031) and reduced the model-based HR from 4.42 for grades I—II to 1.28 for grade III. This factor explained ~73% of between-study heterogeneity (τ^2 reduction from 0.753 to 0.207). Borderline residual heterogeneity (p=0.059) suggests the influence of additional predictors (likely detection method). The data quantitatively support the "initiation and saturation" model. Elevated risk associated with TERT promoter mutation is most pronounced in low-grade tumors. Similarly, the impact of adjusting for CDKN2A/B status and extent of resection on TERT effect size was evaluated as a second covariate. There was an inverse relationship, i.e. accounting for CDKN2A/B significantly reduced HR (β=−1.71; SE 0.77; p=0.063). This association was borderline due to small sample size but it demonstrated a strong modifying effect. For the CDKN2A/B group, analysis of publication bias was limited to a funnel plot **(Fig. 2)**. Despite some signs of asymmetry, association between deletion and prognosis was confirmed in large and small studies.

Discussion

This meta-analysis of 17 studies (n=5867) confirmed the association of TERT mutation and CDKN2A/B deletions with worse overall and disease-free survival. The results demonstrate high consistency with data from individual patient data meta-analysis by Mirian C. et al. (HR 2.77 for overall survival, i.e. almost identical to our result — 2.78) and align with conclusions by Li H.Y. et al. [2, 27, 28].

A key finding of this study is context-dependent nature of these biomarkers supporting "initiation and saturation" hypothesis. TERT mutation is a powerful independent predictor of adverse outcomes (HR ~5.00) in a cohort of grade I and II meningiomas. This is consistent with "initiation effect" model, i.e. activation of mechanisms conferring cellular immortality shifts histologically indolent tumors into category of clinically malignant ones. In contrast, anaplastic (grade III) meningiomas are characterized by insignificant contribution of TERT (HR ~1.5; 95% CI includes 1) despite significant between-group difference (meta-regression, p=0.031) under genomic instability and co-segregation with CDKN2A/B. This aligns with findings from a major multiple-center study (Groff K.J. et al., n=1545) where TERT status was not an independent predictor in overall cohort but remained significant specifically for grade II tumors [9]. CDKN2A/B deletion is the strongest and consistent predictor of recurrence (HR ~5.0—5.8). It is the "gold standard" marker of molecular aggressiveness.

A differentiated algorithm is proposed considering these data. TERT testing should be mandatory for grade I and II meningiomas. Indeed, detection of mutation determines high-risk group necessitating early adjuvant radiotherapy even after gross total resection. For grade III meningiomas, CDKN2A/B testing takes precedence for risk stratification, while TERT status is less important.

Study limitations

The main limitations are retrospective design of trials and high heterogeneity of data (I^2>70% for overall survival) that is partially explained by tumor grade (meta-regression). Small sample sizes and risk of selection bias (focus on recurrences) in some studies could overestimate mutation frequency, while incomplete data on extent of resection do not rule out the influence of surgical factors in specific subgroups.

Conclusion

The TERT promoter mutation and CDKN2A/B deletion are context-dependent markers of poor prognosis in meningiomas. TERT status is the most important in cohort of patients with WHO 2021 grade I and II tumors enabling identification of phenotype with aggressive biological behavior prior to recurrence. In patients with grade III neoplasms, TERT testing should be performed and interpreted together with analysis for CDKN2A/B deletion.

Author contribution:
Concept and design of the study — Sergeev G.S., Nesterchuk M.V., Klimov V.S., Konovalov N.A., Usachev D.Yu., Krivoshapkin A.L.
Collection and analysis of data, statistical analysis — Sergeev G.S.
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Additional materials

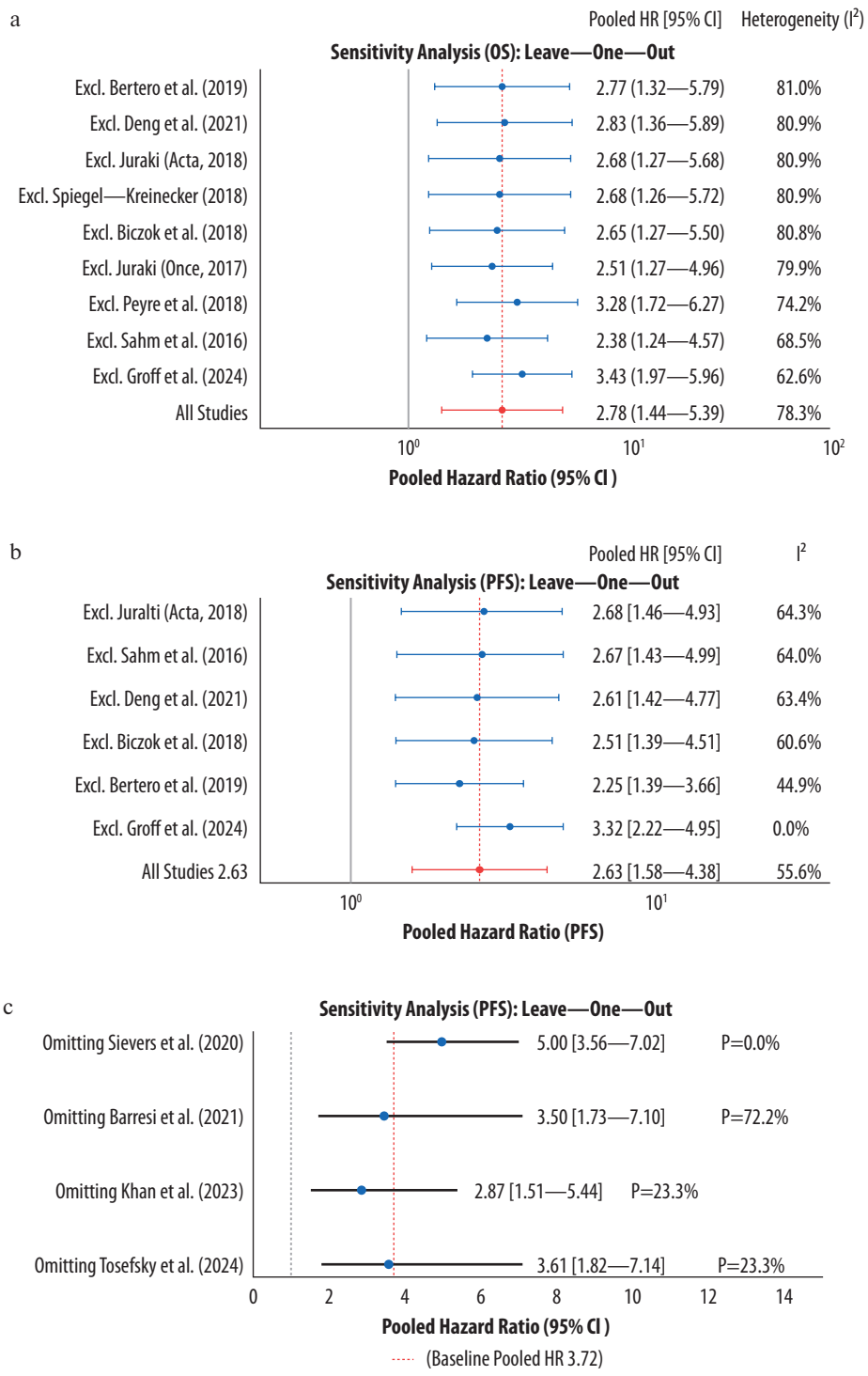

Fig. 1. **Sensitivity analysis plots (sequential exclusion method) for overall and disease-free survival across groups.**

Table 1. **PICOTS inclusion/exclusion criteria (Population, Intervention, Comparison, Outcome)**

Component	Description	Rationale
Population	Adults (>18 years) Any site Grade 1—3	Inclusion of all grades is necessary to evaluate the ability of genetics to reclassify risks
Index	Specific somatic mutations or aberrations, as determined by IHC, FISH, NGS, or Sanger sequencing methods	Covering a wide range of markers enables comparative analysis of predictive power
Comparator	Patients with “wild type”	Control group is required for calculation of relative risks (HR/RR)
Outcome	Primary: Progression-free survival (PFS) Secondary: Overall survival (OS).	PFS is the most direct indicator of biological aggressiveness
Timing	Assessment of prognosis: after surgery. Prognostic horizon: long-term (>3 years)	Short-term studies (<3 years) may underestimate the risks
Setting	Neurosurgical inpatient facilities, cancer hospitals	Data from specialized centers ensure higher quality of surgery and pathomorphology

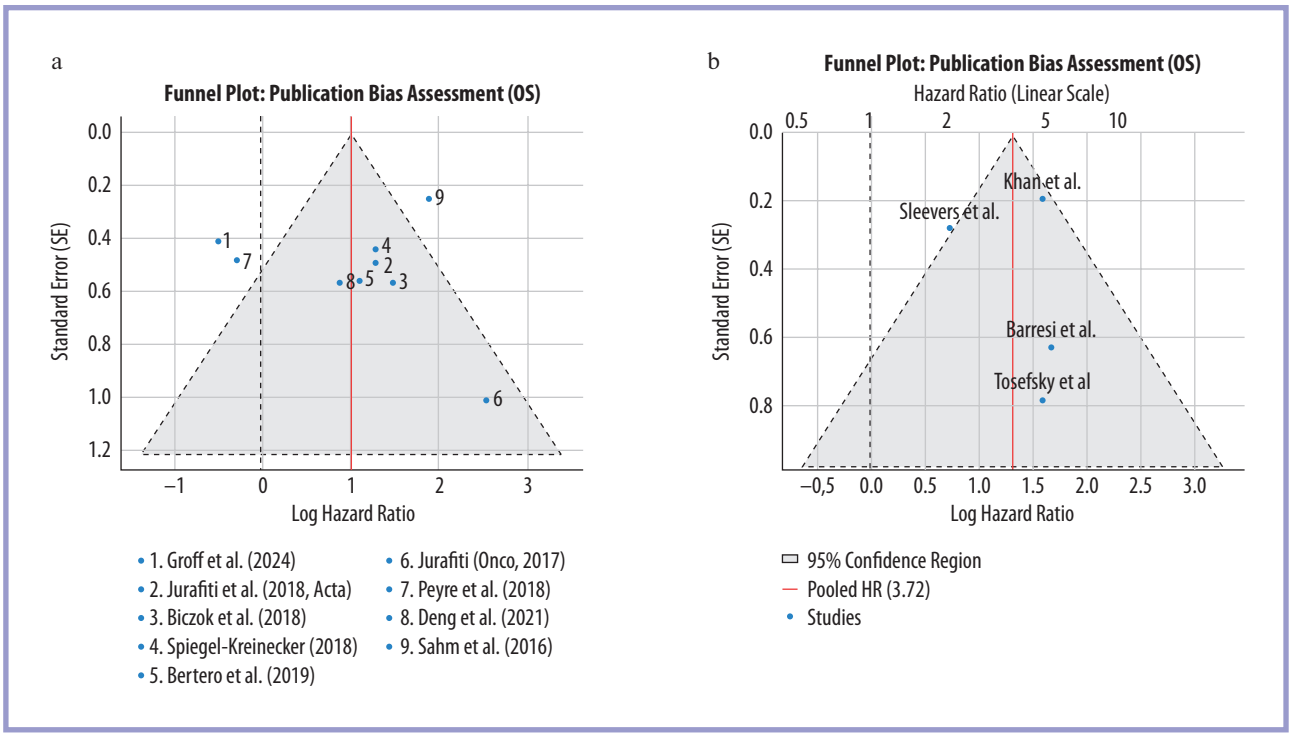

Fig. 2. **Funnel plots for assessing the influence of covariates for groups of articles.**
a — TERT; b — CDKN2A/B.

Table 2. **TERT characteristics of publications**

Study	Groff et al. (2024)	Sahm et al. (2016)	Biczok et al. (2018)	Spiegl-Kreinecker (2018)	Bertero et al. (2019)	Juratli et al. (Acta, 2018)	Juratli et al. (Onco, 2017)	Peyre et al. (2018)	Deng et al. (2021)	Goutagny et al. (2014)
Design	Multiple-center, retrospective	Multiple-center, retrospective	Single-center, retrospective	Single-center, retrospective	Single-center	Cohort (focus on Gr 2 and 3)	Single-center	Multiple-center (focus on Gr3)	Single-center (after RT)	Single-center
Number of patients	1545	252	87	110	152	53	26	57	37	73
Gender (F/M)	1030 F / 515 M	182 F / 70 M	35 F / 52 M	No data	84 F / 68 M	24 F / 29 M	No data	27 F / 30 M	14 F / 23 M	No data
Age (mean)	59 (WT) / 67 (Mut)	56 (WT) / 63 (Mut)	65	>63y assoc. with Mut	61	No data	Variable	60	45	55
WHO G1	951	119	0	32	0	0	3	0	0	30
WHO G2	513	88	72	75	143	39	13	0	32	39
WHO G3	81	45	15	21	9	14	10	57	5	16
Resection (GTR/STR)	1041 GTR / 329 STR (Info avail)	No data	42 GTR / 45 STR	No data	No data	not applicable	Multiple recurrences	43 GTR / 11 STR	20 GTR / 17 STR	No data
TERT Mut (*n*, %)	64 (4.1%)	16 (6.4%)	6 (6.9%)	8 (7.2%)	5 (8%) in sequenced subset	10 (18.8%)	6 (23%)	8 (14%)	8 (22%)	6 patients (8%)
Co-alterations	CDKN2A/B (31.7% in Mut), 1p loss (77.2%), NF2	Not analyzed	Brain invasion (100% in Mut)	TERT promoter methylation	Ki67 hotspots, necrosis, SSTR2a	DMD deletions (32%), NF2	LPCAT1-TERT fusion	TERT methylation (91%)	NF2 (59%), ATRX (35%)	NF2
PFS (months)	15.0 (Mut) vs Not Reached (G1 WT)	10.1 (Mut) vs 179.0 (WT)	12.5 (Mut) vs 27 (WT)	Early recurrence (p=0.0003)	Not reported for TERT specifically	Not reported	13.2 (Mut) vs 43.2 (WT)	Significant in secondary G3 only	25 (Mut) vs 77 (WT)	No data
OS (months)	42.8 (Mut) vs 182.1 (G1 WT)	No data	26 (Mut) vs 46 (WT)	53.8 (Mut) vs 115.6 (WT)	Significantly shorter (p=0.014)	61.2 (Mut) vs 222 (WT)	32.4 (Mut) vs 129.6 (WT)	No significant difference	66 (Mut) vs 85 (WT)	No data
HR OS (95% CI)	0.62 (0.28—1.38)*	6.62 (4.08—10.63)**	4.37 (1.44—13.26)	3.78 (1.58—9.08)	2.99 (1.01—8.86)	3.8 (1.5—9.9)	12.74 (1.77—91.8)	0.76 (0.30—1.94)	2.51 (0.83—7.63)**	—
HR PFS (95% CI)	1.11 (0.62—1.97)*	2.7 (1.2—6.0)	3.58 (1.50—8.56)	No data	5.98 (2.24—15.97)	2.6 (1.0—6.6)	No data	No data	3.0 (1.2—7.5)**	—

Table 3. **Characteristics of publications on CDKN2A/B**

Parameter	Sievers et al. (2020)	Barresi et al. (2021)	Tosefsky et al. (2024)	Khan et al. (2023)	Driver et al. (2022)	Wang et al. (2023)	Sasaki et al. (2022)
Study design	Retrospective (DNA methylation)	Retrospective (22 atypical)	Retrospective (15 Grade 3)	Retrospective (776 methyl/RNA)	Retrospective (527 integr.)	Multiple-center (1577 omics)	Retrospective (MTAP IHC)
Total number of patients	528	22	15	776	527	1577	30
Ggender (♀/♂)	350♀ / 178♂	12♀ / 10♂	8♀ / 7♂	466♀ / 310♂	67%♀ / 33%♂	—	18♀ / 12♂
Age (years, median)	57	68	64 (IQR: 48-73.5)	57	57	—	68
WHO Gr 1	238	0	0	474	326	—	0
WHO Gr 2	220	22	0	139	172	—	27
WHO Gr 3	70	0	15	15	29	Not specified	3
Extent of resection	Not specified	Simpson 1—3	Simpson 2—5	Simpson 1—4	Simpson 1—4	GTR/STR	Not specified
CDKN2A/B status (details)	26 (4.9%): 7 Gr2, 19 Gr3	1 homozygous, 7 heterozygous	3 homozygous, 2 heterozygous	38 del (11 homozygous / 15 heterozygous)	28 (5.3%)	108 (7.1%)	5 homozygous
Concomitant changes		NF2, 18q-deletion	TERTp-mut, BAP1-loss	loss 1p/22q	1p, 14q, 18q loss	CDKN2A/CDK4 expression	Loss of MTAP expression
PFS (months, median)	8 (homo) vs 101 (WT)	12 (recurrence) vs 72 (No Rec)	11 (CDKN2A-del) vs 101 (WT)	11 (Homo) vs 25 (Het) vs 61 (WT)	11 (CDKN2A-del) vs 47 (WT)	18 (CDKN2A-high) vs 60 (Low)	9 (MTAP loss) vs 50 (Intact)
OS (months, median)	—	—	22 (CDKN2A-del) vs 123 (WT)	—	28 (Int. Gr3) vs 120 (Gr1)	36 (CDKN2A-high) vs 96 (Low)	51 (MTAP loss) vs 84 (Intact)
Prognostic markers	CDKN2A/B-del, methyl. class	18q-del, CDKN2A/B-del	TERTp, CDKN2A/B, BAP1	CDKN2A/B-del, group C	Integrated Gr, CDKN2A	CDKN2A, CDK4 expression	MTAP (CDKN2A surrogate)
HR for PFS (95% CI)	2.06 [1.20—3.53] (p=0.009)	5.30 [1.5—18.2]	Heterozygous 3.57 [0.65—19.6] Homozygous 4.91 [1.04—23.1] P=0.039	4.98 homozygous, 3.63 for heterozygous	2.16	Heterozygous 3.63 [2.38—5.5] Homozygous 4.98 [3.46—7.15] P<0.001	$p < 0.001$
HR for OS (95% CI)	—	—	Heterozygous. 3.73 [0.68—20.5] Homozygous 5.84 [1.16—29.4] (p=0.032)	3.73 (Hetero, p=0.13)	4.1	-	p=0.01

Table 4. **Demographic indicators in articles**

Category	Value and key features
Sex ratio	F:M (2:1). Imbalance is neutralized in aggressive subtypes and recurrences
Median of age	With TERT mutation: 63—67 years; Without TERT mutation: 56—59 years; CDKN2A/B: 57—68 years
Histological distribution	Grade 1: 1135 cases (47.4%); Grade 2: 1014 cases (42.4%); Grade 3: 273 cases (11.4%)
Incidence of TERT mutation	Overall: 5.7% (137 cases); Unselected cohorts: 4.1—6.4%; Aggressive and recurrent tumors: 18.8—23.0%

Table 5. **Extent of surgery**

Category / Study group	Value and key features	
TERT GTR (Simpson 1—3)	Resection data are available for 1548 patients 1146 patients (74%)	
STR (Simpson 4—5)	402 patients (26%)	
CDKN2A/B GTR	2917 patients from 67% (Tosefsky) to 100% (Barresi). Majority in large series (Wang, Driver)	
STR	33%	Associated with a difficult-to-access location or invasive tumor growth