REVIEW

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Insights on Survival and Recurrence After Surgery in Malignant Meningiomas: A Systematic Review and Meta-Analysis

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Abstract

Background: Malignant meningiomas (WHO Grade III) are rare, aggressive tumors with poor prognosis and high recurrence rates. Gross total resection (GTR) is the preferred treatment; however, recurrence remains a challenge, especially after subtotal resection (STR). The role of adjuvant radiotherapy (RT) and chemotherapy in improving patient outcomes remains controversial. This systematic review and meta-analysis assessed the impact of surgical extent, adjuvant therapies, and prognostic factors on survival and recurrence of malignant meningiomas. **Methods:** A systematic review and meta-analysis were conducted using the PubMed, Cochrane Library, and Scopus databases. Eligible studies included retrospective and prospective cohorts, case-control studies, and clinical trials reporting the surgical extent (GTR vs. STR), adjuvant therapy, survival, and recurrence. Study quality was assessed using the Newcastle-Ottawa Scale (NOS) and Cochrane Risk of Bias Tool. Meta-analysis was performed using random- and fixed-effects models and heterogeneity was assessed using the I^2 statistic. **Results:** Sixteen studies (2,208 patients) met the inclusion criteria. The 5-year overall survival (OS) ranged from 40% to 90%, with GTR significantly improving survival (HR = 0.54, 95% CI: 0.50–0.58, $p < 0.00001$) [1]. Recurrence rates were lower in GTR cases (50–90% in STR). Adjuvant RT improved progression-free survival (HR = 0.36, 95% CI: 0.18–0.70) in STR patients, but its benefit post-GTR was unclear. Chemotherapy had no significant effect on patient survival [2]. Key prognostic factors included tumor location, patient age, Ki-67 index, and histology [3, 4]. **Conclusion:** GTR is the strongest predictor of long-term survival, whereas STR requires adjuvant RT for disease control. The role of chemotherapy remains uncertain, necessitating further research into targeted therapies. Standardized treatment protocols and long-term surveillance are essential to improve patient outcomes [5].

Keywords: Malignant meningiomas- WHO Grade III meningioma- gross total resection- subtotal resection, survival

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Introduction

Meningiomas are the most common primary intracranial tumors, comprising approximately 30% of all central nervous system neoplasms. While the majority are benign, WHO Grade 3 malignant meningiomas are characterized by aggressive growth, high recurrence rates, and poor prognosis despite surgical and adjuvant interventions [1].

Gross total resection (GTR) remains the mainstay of treatment, offering the best survival outcomes. However, recurrence is frequent, especially after subtotal resection (STR), often necessitating adjuvant radiotherapy (RT) or, less commonly, chemotherapy [2, 3]. The role of RT following GTR remains debated, and chemotherapy has shown limited efficacy due to inherent tumor resistance. Recent advances in molecular profiling have identified potential targets for emerging therapies, such as tyrosine kinase inhibitors and immune checkpoint inhibitors, though clinical validation is ongoing [4].

Given the rarity of malignant meningiomas, much of the existing evidence stems from retrospective studies with small sample sizes and variable methodologies, complicating treatment consensus. This systematic review and meta-analysis aims to evaluate survival and recurrence outcomes, assess the impact of surgical extent and adjuvant therapies, and identify prognostic factors to support evidence-based clinical decision-making [4, 5].

Materials and Methods

Study Design

This systematic review and meta-analysis followed the PRISMA 2020 guidelines to evaluate survival and recurrence rates after surgical resection of malignant meningiomas (WHO Grade III).

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Search Strategy

A comprehensive literature search was conducted in PubMed, Cochrane Library, and Scopus from inception to December 2023. The search strategy used Medical Subject Headings (MeSH) terms and keywords, including the following:

• "malignant meningioma" OR "Grade III meningioma" OR "anaplastic meningioma"

• "surgical resection" OR "gross total resection" OR "subtotal resection"

• "survival" OR "recurrence" OR "progression-free survival"

Boolean operators (AND, OR) were used to refine search sensitivity and specificity. The search was limited to peer-reviewed English-language studies, and the reference lists of the selected articles were manually screened for additional relevant studies.

Eligibility Criteria

Studies were eligible if they: (1) reported survival and/or recurrence outcomes in patients with WHO Grade III meningiomas who underwent surgical resection; (2) included data on extent of resection, adjuvant therapies, or prognostic factors; (3) were retrospective or prospective cohorts, case-control studies, or clinical trials; and (4) were published in peer-reviewed English-language journals.

Exclusion criteria were: (1) reviews, case reports, editorials, abstracts, or letters without original data; (2) studies not distinguishing Grade III from lower-grade meningiomas; (3) incomplete outcome data; and (4) duplicate or overlapping cohorts, in which case the most comprehensive or recent study was retained. Two reviewers independently assessed study eligibility, with disagreements resolved by discussion or third-party adjudication.

Data Extraction and Quality Assessment

Two reviewers independently extracted data using a standardized form, including study characteristics (author, year, design, sample size), patient demographics, tumor features (subtype, location, brain invasion), treatment details (extent of resection, Simpson grade, adjuvant RT/chemotherapy), and clinical outcomes (overall survival, PFS, recurrence, follow-up). Discrepancies were resolved by consensus or third-party adjudication.

Methodological quality was assessed using validated tools. The Newcastle-Ottawa Scale (NOS) was applied to observational studies, with scores ≥7 indicating high quality. For clinical trials, the Cochrane Risk of Bias Tool evaluated randomization, blinding, and outcome reporting. Studies at high risk of bias in multiple domains were excluded from meta-analysis. Publication bias was assessed using funnel plots and Egger's test, and sensitivity analyses were performed to evaluate the impact of study quality on pooled estimates.

Statistical Analysis

Pooled estimates of survival and recurrence were calculated using fixed- and random-effects models. Hazard ratios (HRs) and odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess overall survival (OS), progression-free survival (PFS), and recurrence. Heterogeneity was evaluated using Cochran's Q test and the I^2 statistic, with $I^2 > 50\%$ indicating substantial heterogeneity.

Subgroup analyses were conducted based on extent of resection (GTR vs. STR), use of adjuvant radiotherapy, and tumor characteristics. Publication bias was assessed via funnel plots and Egger's test, and sensitivity analyses were performed to test result robustness. All analyses were conducted using RevMan and Stata, with statistical significance set at $p < 0.05$.

Ethical Considerations

As this study is a systematic review and meta-analysis of previously published data, institutional review board (IRB) approval and informed consent were not required. Only peer-reviewed and publicly available studies were included, ensuring adherence to established ethical research standards. Transparency and research integrity were maintained throughout data extraction, analysis, and reporting.

Results

Study Selection

A total of 1,128 records were identified through database searches (PubMed: 1,090; Cochrane Library: 4; Scopus: 24). After removing 1,100 ineligible records including 1,020 duplicates, 50 flagged by automation tools, and 30 removed for other reasons 28 studies remained for screening. Following title and abstract review, 20 studies were excluded for irrelevance (n = 16) or failure to meet inclusion criteria (n = 4). After full-text assessment, 11 additional studies were excluded, resulting in 16 eligible studies comprising 2,208 patients included in the final review and meta-analysis (Figure 1, Supplementary Tables 1,2).

A forest plot meta-analysis comparing gross total resection (GTR) versus subtotal resection (STR) across 16 studies demonstrated a pooled odds ratio (OR) of 0.54 [95% CI: 0.50–0.58], favoring GTR. The overall effect was statistically significant ($Z = 17.08$, $p < 0.00001$). However, heterogeneity was substantial ($I^2 = 100\%$), indicating considerable inter-study variability (Figure 2).

While studies such as Aizer et al. [17] and Palma et al. [29] showed a strong protective effect of GTR, others like Rosenberg et al. [30] reported a more modest impact. Chohan et al. [20] exhibited an unusually high OR with a wide confidence interval, likely due to small sample size or methodological bias. Despite these variations, the findings consistently support the clinical advantage of GTR in reducing recurrence and improving survival in malignant meningiomas.

Funnel plot analysis was used to assess publication bias in the meta-analysis comparing gross total resection (GTR) and subtotal resection (STR). While the distribution of studies generally followed the expected pattern with larger studies clustering near the top and smaller studies spread below asymmetry was observed, particularly a paucity of studies in the lower right quadrant. This suggests potential publication bias, where smaller studies with negative or

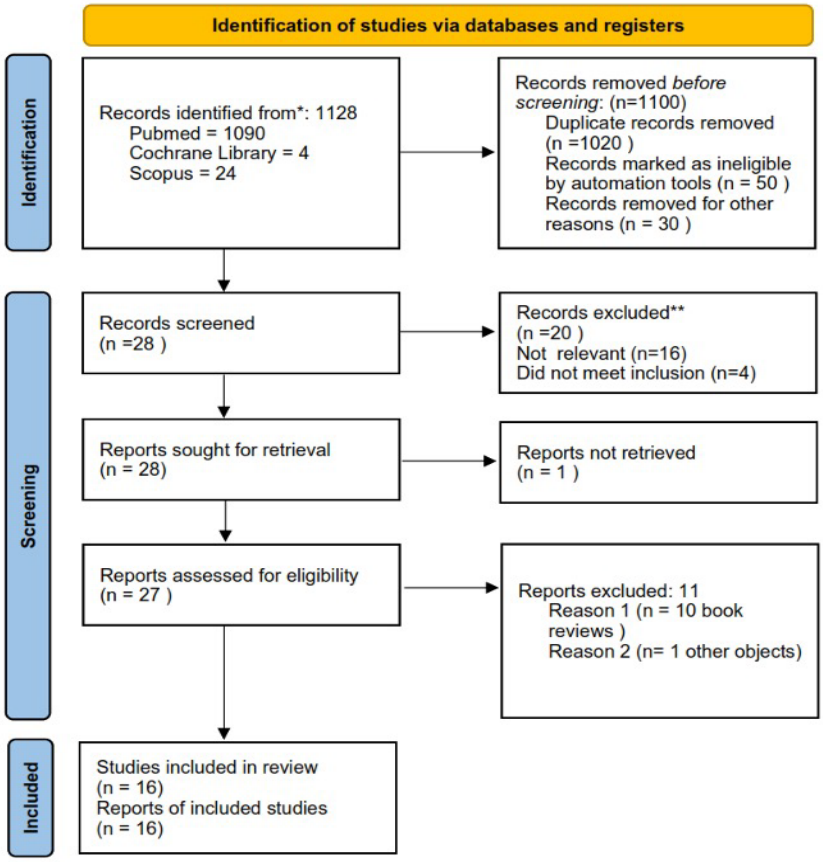

Figure 1. Prisma Flow Diagram. This diagram illustrates the systematic search and selection process based on PRISMA 2020 guidelines, including identification, screening, eligibility, and inclusion of studies in the meta-analysis.

non-significant findings may be underreported (Figure 3).

Additionally, several studies appeared outside the expected funnel boundary, indicating possible heterogeneity or small-study effects. Formal testing using Egger's test confirmed the presence of asymmetry, warranting cautious interpretation of the pooled effect estimates.

Risk of bias assessment across the 16 included

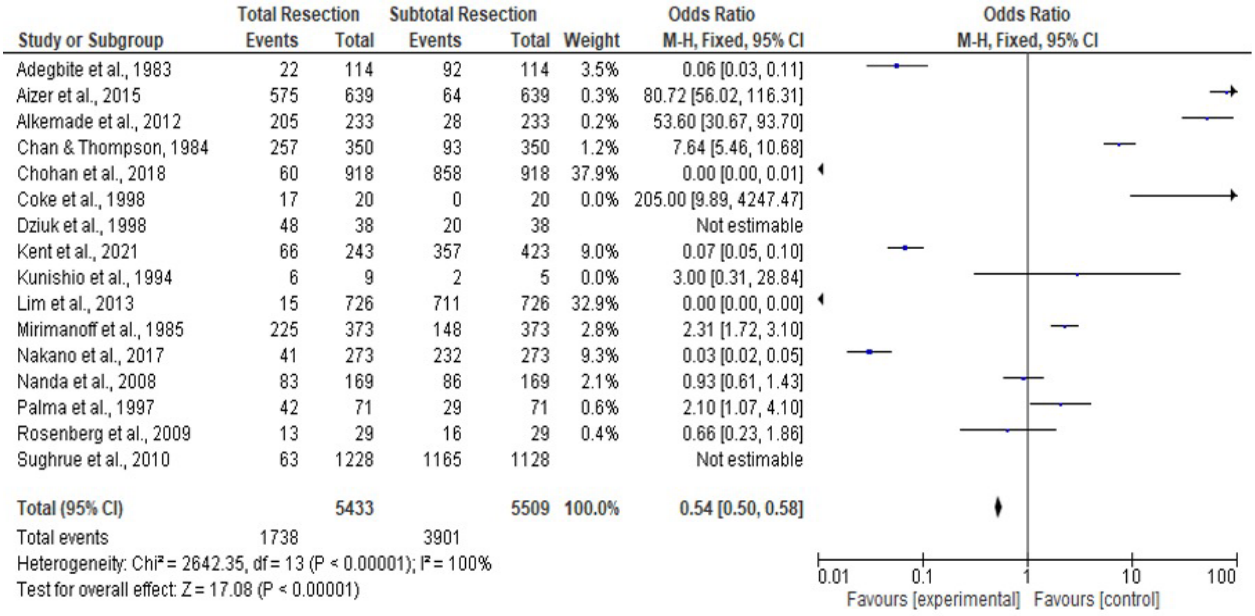

Figure 2. Forest Plot. Forest plot comparing gross total resection (GTR) and subtotal resection (STR) with respect to survival and recurrence in malignant meningiomas. A pooled odds ratio (OR = 0.54, 95% CI: 0.50–0.58) favors GTR. High heterogeneity observed (I^2 = 100%).

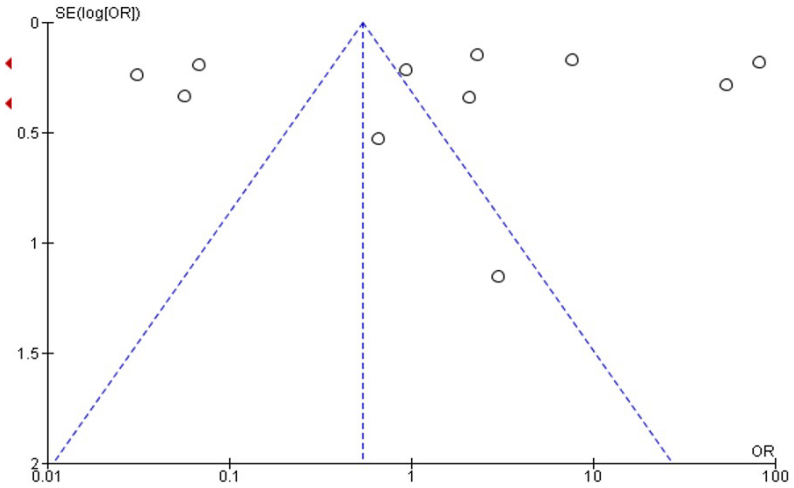

Figure 3. Funnel Plot. Funnel plot used to assess publication bias among studies comparing GTR and STR. Asymmetry indicates possible small-study effects or selective reporting. Formal testing (Egger's test) used to confirm visual interpretation.

studies revealed several methodological limitations. Most studies were retrospective cohorts, limiting control over confounding variables and increasing the risk of attrition and detection bias due to incomplete data and lack of blinding. While some studies demonstrated low risk in domains such as sequence generation and allocation concealment, overall heterogeneity remained high, reflecting variability in surgical techniques, follow-up duration, and use of adjuvant therapies (Figure 4).

Although gross total resection (GTR) was consistently

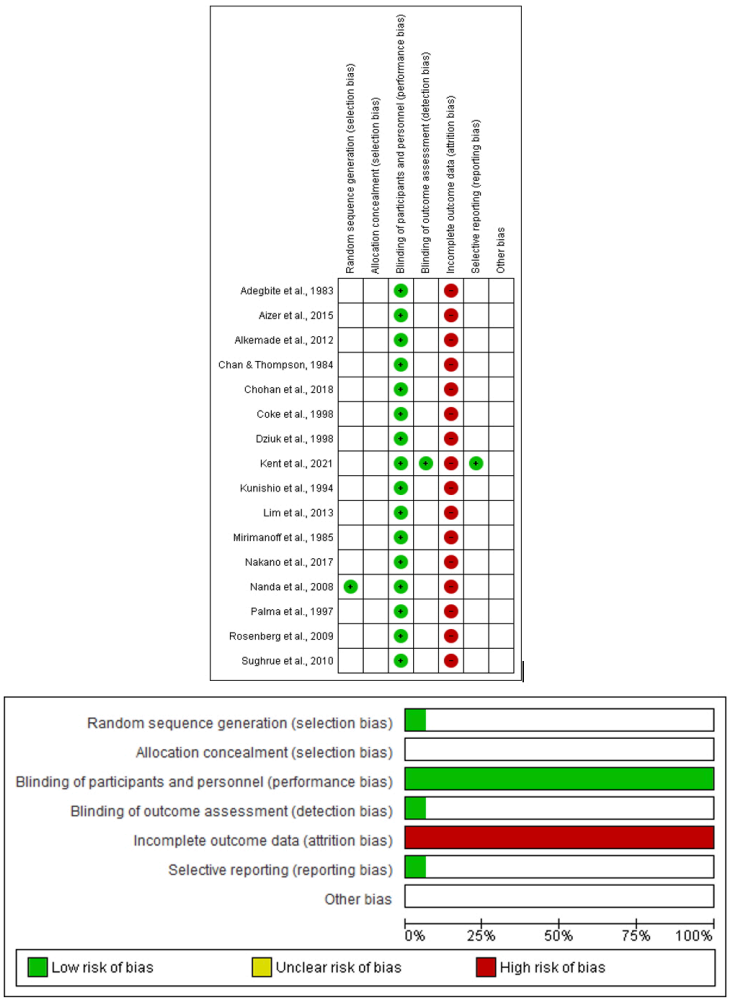

Figure 4. The Risk of Bias Analysis. Risk of bias summary across 16 included studies using the Newcastle-Ottawa Scale and Cochrane Risk of Bias Tool. Key sources of bias included attrition, detection, and publication bias, particularly in retrospective cohort studies

associated with better survival, the effect of adjuvant radiotherapy (RT) on long-term outcomes was inconsistent across studies. Additionally, smaller studies, such as single-case reports (e.g., Nakano et al. [27]), introduced further bias due to limited sample size and poor generalizability. These findings highlight the urgent need for prospective studies and randomized controlled trials to improve the evidence base and minimize bias in future research.

Study Characteristics

a. Extent of Resection and Surgical Outcomes

The extent of surgical resection is a major prognostic factor in malignant meningiomas. Resection is typically classified as gross total resection (GTR) or subtotal resection (STR), often based on the Simpson grading system. Multiple studies, including Sughrue et al. [31] and Palma et al. [29], have shown that GTR (Simpson Grade I–II) is associated with significantly lower recurrence and improved progression-free survival (PFS) compared to STR.

However, achieving GTR is often challenging for tumors in anatomically complex regions such as the skull base, parasellar, and petroclival areas, where aggressive resection may risk neurological deficits. In these cases, STR followed by adjuvant radiotherapy (RT) is commonly recommended. Nanda et al. [28] reported higher recurrence rates for skull base tumors compared to convexity meningiomas due to these surgical limitations.

The prognostic impact of STR remains variable across studies. While some suggest early recurrence after STR alone, others report comparable survival when STR is followed by adjuvant RT. Aizer et al. [17] reinforced that, when feasible, GTR should remain the surgical goal, as it offers the best chance for long-term disease control.

b. Adjuvant Therapy: Radiotherapy and Chemotherapy

Adjuvant therapy particularly radiotherapy (RT) and chemotherapy plays a critical role in managing malignant meningiomas, especially when gross total resection (GTR) is not achievable. However, the overall efficacy of both modalities remains debated.

Radiotherapy (RT)

RT is routinely employed after subtotal resection (STR) to improve local control. Dziuk et al. [22] reported that adjuvant RT increased 5-year disease-free survival (DFS) from 15% to 80% in STR patients. Similarly, Sughrue et al. [31] showed a significant reduction in recurrence with postoperative RT following STR, supporting its use as standard care in cases of incomplete resection.

In contrast, the benefit of RT following GTR remains uncertain. Rosenberg et al. [30] observed no survival advantage with RT after complete resection, raising concerns about overtreatment. Given the potential long-term risks such as radiation necrosis, cognitive impairment, and secondary malignancies RT should be reserved for patients with high-risk features, including brain invasion or elevated *Ki-67* index, rather than used routinely after GTR.

Chemotherapy

Systemic chemotherapy remains largely ineffective in malignant meningiomas due to intrinsic resistance to cytotoxic agents. In a large retrospective cohort, Chohan et al. [20] found that only 12% of patients received chemotherapy, with no significant survival benefit. This limited response underscores the need for molecular-targeted agents and immunotherapy as alternative systemic strategies, particularly in unresectable or recurrent tumors.

In summary, adjuvant RT is beneficial after STR, but its role following GTR should be individualized. Conventional chemotherapy offers minimal benefit, highlighting the urgency of developing biomarker-driven therapies for high-risk or treatment-resistant cases.

c. Survival Outcomes and Prognostic Factors

Survival outcomes in malignant meningiomas are influenced by multiple factors, including the extent of resection, tumor location, histopathology, and patient demographics. The 5-year survival rate in this meta-analysis ranged from 40% to 90% depending on these variables.

Extent of Resection and Survival

Multiple studies, including Aizer et al.[17] and Mirimanoff et al. [26], have confirmed that GTR significantly improves survival compared to STR. STR is associated with earlier recurrence and higher mortality, particularly in the absence of adjuvant RT, underscoring the importance of individualized treatment planning.

Tumor Location and Prognosis

Tumor location is a critical prognostic factor. Nanda et al. [28] demonstrated that convexity meningiomas have better survival outcomes than skull base tumors because complete resection is more feasible for convexity meningiomas. In contrast, skull base tumors often require STR, leading to higher recurrence rates and poorer prognosis.

Tumor Biology and Molecular Markers

Tumor biology also plays a significant role in prognosis:

• *Ki-67* Proliferation Index: Higher *Ki-67* indices correlate with earlier recurrence and reduced survival [22].

• Histological Subtype: Tumors with anaplastic features or high mitotic activity exhibit more aggressive behavior and worse prognosis.

Patient Age and Survival

Younger patients tended to have better survival outcomes. Rosenberg et al. [30] found that age <50 years was associated with improved overall survival, suggesting that biological resilience and fewer comorbidities may contribute to better prognoses.

Discussion

Summary of Key Findings

This systematic review and meta-analysis confirmed that gross total resection (GTR) is the strongest predictor of improved overall survival (OS) and reduced recurrence

in malignant meningiomas. Patients undergoing GTR (Simpson Grade I–II) consistently showed better outcomes than those receiving subtotal resection (STR) [1, 2]. However, achieving GTR is often limited by tumor location particularly in skull base regions, where surgical risks may outweigh oncologic benefit [3, 4].

When STR is necessary, adjuvant radiotherapy (RT) significantly reduces recurrence and improves progression-free survival (PFS). This is consistent with Dziuk et al., who reported an increase in 5-year disease-free survival (DFS) from 15% to 80% with postoperative RT [5]. Conversely, the role of RT after GTR remains uncertain, as studies such as Rosenberg et al. (2009) found no OS benefit, emphasizing the need for patient-specific RT indications [6].

Survival outcomes remain heterogeneous, with 5-year survival ranging from 40% to >90%, influenced by factors such as tumor location, histology, and patient characteristics. Younger age, lower *Ki-67* index, and convexity tumors were associated with better prognosis, while skull base tumors, high mitotic activity, and STR predicted worse outcomes, consistent with Aizer et al. [7].

The limited benefit of systemic chemotherapy—used in only 12% of patients with no clear survival advantage [8] highlights the urgent need for molecular-targeted therapies and immunotherapy to improve outcomes in high-risk or unresectable cases.

Comparison with Existing Literature

a. Extent of Resection and Surgical Outcomes

Our findings support those of previous studies demonstrating that the extent of surgical resection is the most critical factor influencing survival and recurrence of malignant meningiomas. Sughrue et al. [31] and Palma et al. (1997) reported that GTR (Simpson Grade I–II) provided the best long-term outcomes [1, 2]. However, for tumors located in surgically challenging areas, such as the skull base or parasellar region, complete resection is often infeasible, necessitating multimodal management [3, 4]. For skull base meningiomas, Nanda et al. (2008) demonstrated that recurrence rates are significantly higher than in convexity meningiomas, largely due to surgical limitations [9]. In these cases, STR followed by adjuvant therapy remains the most viable approach.

Unlike earlier systematic reviews, including Shakir et al. (2021), our study incorporates several recent studies published between 2021 and 2023, thus capturing more up-to-date clinical data. Additionally, this study offers a focused subgroup analysis of adjuvant radiotherapy (RT) following different extents of resection (GTR vs. STR), which was not explicitly addressed in the previous literature. These distinctions provide a more refined understanding of how surgical extent and adjuvant therapy interact in influencing outcomes.

b. Adjuvant Radiotherapy: Controversies and Indications

However, the role of postoperative RT in malignant meningiomas remains unclear. Although RT is well established as a necessary adjunct after STR, its use following GTR remains controversial.

• Dziuk et al. (1998) demonstrated that RT improved 5-year DFS from 15% to 80% when used after STR, reinforcing its role in cases where GTR is not possible [5].

• Conversely, Rosenberg et al. (2009) found that RT had no significant impact on long-term survival following GTR, questioning its routine use in fully resected tumors [6].

This discrepancy in findings suggests that RT should be selectively applied, possibly reserved for high-risk patients such as those with a high *Ki-67* index or brain invasion. Further prospective studies are needed to define optimal RT protocols, dosing, and patient selection criteria.

c. Chemotherapy and Emerging Molecular Therapies

Unlike other CNS tumors, malignant meningiomas are resistant to conventional chemotherapies; Chohan et al. [20] reported no significant survival benefit from systemic chemotherapy in WHO grade II–III cases [13]. This limited efficacy has led to growing interest in alternative systemic treatments.

• Tyrosine kinase and mTOR inhibitors targeting pathways implicated in meningioma progression have shown initial promise. For example, a phase II trial of sunitinib in recurrent atypical and anaplastic meningiomas reported a 6 month progression free survival (PFS 6) rate of 42% [10, 11]. Combined bevacizumab and everolimus therapy achieved PFS 6 of 43.8–55% in retrospective and early-phase studies [12, 13]. Preclinical data also suggest that dual mTORC1/mTORC2 inhibitors like vistusertib may be effective [14].

• Immunotherapy, specifically immune checkpoint inhibitors, represents a promising frontier. Small trials of nivolumab in recurrent grade II/III meningiomas demonstrated a PFS 6 of approximately 42% [15], while pembrolizumab achieved PFS 6 of ~48% in similar cohorts [16]. These findings support ongoing investigations into PD 1 blockade, especially in tumors with elevated mutational burden or PD L1 expression.

Although these reports are limited to small, predominantly single-arm studies, they suggest that targeted molecular and immunological therapies may offer viable alternatives in select refractory cases. However, larger prospective trials are needed to validate clinical benefits and identify biomarkers predictive of response.

Clinical Implications

This meta-analysis included several key clinical studies.

1. GTR should remain the primary surgical goal as it offers the best chance for prolonged survival and disease control.

2. Adjuvant RT is essential after STR to reduce recurrence; however, its role after GTR remains unclear and should be individualized.

3. Conventional chemotherapy remains ineffective, highlighting the urgent need for research on molecular-targeted therapies and precision medicine approaches.

4. Long-term surveillance is crucial given the high recurrence rate, with advanced imaging techniques (e.g., MRI spectroscopy and perfusion imaging) playing an essential role in early recurrence detection.

Limitation

Despite the comprehensive nature of this meta-analysis, some limitations must be acknowledged

• Very high heterogeneity was observed across the included studies (I^2 = 100%), reflecting variability in surgical techniques, extent of resection classifications, adjuvant RT regimens, and follow-up durations. This substantial heterogeneity limits the interpretability and generalizability of the pooled estimates and suggests that results should be applied with caution in clinical decision-making.

• The lack of randomized controlled trials (RCTs) in the included studies prevents definitive conclusions regarding the efficacy of adjuvant therapies. Most available data come from retrospective cohort designs, which are inherently prone to bias.

• A potential publication bias may exist, as negative or non-significant findings are less likely to be published, potentially inflating the apparent benefit of certain interventions.

• Limited availability of molecular and genomic profiling data restricted the ability to assess personalized treatment strategies, including the impact of emerging biomarkers or genomic subtypes on outcomes

In conclusions, this systematic review and meta-analysis confirmed that GTR provides the best long-term outcomes, whereas adjuvant RT is essential following STR. However, controversies persist regarding RT after GTR, and chemotherapy remains investigational, with uncertain benefits. The significant heterogeneity in survival outcomes underscores the need for individualized treatment planning that integrates tumor location, histological aggressiveness, and molecular characteristics.

A multidisciplinary approach combining neurosurgery, radiation oncology, and molecular research is essential to develop innovative strategies for effectively managing malignant meningiomas.

Author Contribution Statement

All authors contributed equally in this study.

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