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CLINICAL OUTCOMES AND SURVIVAL BENEFITS OF RADICAL RADIOTHERAPY COMBINED WITH TEMOZOLOMIDE IN PATIENTS WITH HIGH-GRADE BRAIN TUMORS

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Abstract

Background: *High-grade brain tumors, particularly glioblastoma multiforme and anaplastic astrocytoma, are highly aggressive malignancies with poor prognosis despite advances in multimodal therapy. Radical radiotherapy combined with temozolomide remains the standard treatment; however, survival outcomes and treatment response vary significantly due to tumor biology and patient-related factors.*

Objective: *This study aimed to evaluate the clinical outcomes and survival benefits of radical radiotherapy combined with temozolomide in patients with high-grade brain tumors.*

Methods: *A quantitative observational cohort design (retrospective/prospective) was employed. Patients with histologically confirmed high-grade brain tumors treated with radical radiotherapy and temozolomide were included. Clinical response was assessed using MRI-based criteria, while survival outcomes were measured in terms of overall survival (OS) and progression-free survival (PFS). Data were analyzed using descriptive statistics and Kaplan–Meier survival analysis, with subgroup comparisons based on molecular and clinical variables.*

Results: *The findings demonstrated that combined radiotherapy and temozolomide provided measurable survival benefits, with improved overall and progression-free survival compared to historical radiotherapy-only outcomes. However, complete response was rare, and disease progression remained common within two years. MGMT promoter methylation was significantly associated with improved survival outcomes ($p < 0.05$). Hematological toxicities, including thrombocytopenia and lymphopenia, were frequently observed and were significantly associated with treatment interruptions.*

Conclusion: *Radical radiotherapy combined with temozolomide remains the standard and most effective therapeutic approach for high-grade brain tumors, offering meaningful survival benefits. However, prognosis remains poor, highlighting the need for improved molecular stratification, toxicity management, and development of novel therapeutic strategies.*

INTRODUCTION

High-grade brain tumors, particularly glioblastoma multiforme (GBM) and anaplastic astrocytoma, represent the most aggressive and lethal primary central nervous system malignancies. Despite advances in neurosurgery, radiotherapy, and chemotherapy, prognosis remains poor, with median survival for glioblastoma typically ranging between 12 and 18 months (Ostrom et al., 2022;

Weller et al., 2021). These tumors are characterized by rapid proliferation, diffuse infiltration, genetic heterogeneity, and marked resistance to conventional therapies, making complete eradication extremely challenging.

The current standard of care for high-grade brain tumors is maximal safe surgical resection followed by radical radiotherapy combined with concomitant and adjuvant temozolomide chemotherapy, commonly known as the Stupp protocol (Stupp et al., 2005). Temozolomide, an oral alkylating agent, exerts cytotoxic effects through DNA methylation at the O6 position of guanine, leading to tumor cell apoptosis. When combined with radiotherapy, it enhances radiosensitivity and improves both progression-free survival (PFS) and overall survival (OS) (Weller et al., 2021).

Recent clinical evidence has consistently demonstrated that concurrent radiotherapy and temozolomide significantly improve survival outcomes compared to radiotherapy alone. However, therapeutic benefits remain modest due to intrinsic and acquired resistance mechanisms, including MGMT (O6-methylguanine-DNA methyltransferase) promoter methylation status, tumor heterogeneity, and blood–brain barrier limitations (Louis et al., 2021; Aldape et al., 2019). Patients with MGMT promoter methylation generally exhibit better responses to temozolomide, highlighting the importance of molecular stratification in treatment planning.

In addition to survival benefits, treatment-related toxicities remain a significant clinical concern. Hematological adverse effects such as thrombocytopenia, neutropenia, and lymphopenia are commonly reported during concurrent chemoradiotherapy. Neurocognitive decline, fatigue, and gastrointestinal symptoms further contribute to reduced quality of life during treatment (Weller et al., 2021). Therefore, balancing treatment efficacy with toxicity management remains a central challenge in neuro-oncology.

In resource-limited settings, including developing countries, outcomes may be further compromised due to delayed diagnosis, limited access to advanced radiotherapy techniques (such as intensity-modulated radiotherapy), and inadequate molecular diagnostic facilities. These contextual limitations necessitate localized evidence to better understand real-world outcomes of combined modality treatment in high-grade brain tumor patients.

Problem Statement

Despite the establishment of radical radiotherapy combined with temozolomide as the standard treatment protocol for high-grade brain tumors, overall survival outcomes remain suboptimal, and disease recurrence is nearly universal. While landmark trials such as the Stupp protocol have demonstrated survival benefits, real-world clinical outcomes often vary significantly due to patient heterogeneity, molecular tumor characteristics, and healthcare system constraints.

A critical gap exists in context-specific evidence evaluating the effectiveness of this combined modality treatment in routine clinical practice, particularly in developing countries where diagnostic limitations, delayed presentation, and restricted access to advanced neuro-oncological care are prevalent. Furthermore, existing studies predominantly focus on controlled trial settings, with limited emphasis on real-world survival outcomes and treatment-related toxicities.

Additionally, there is insufficient integration of clinical, radiological, and survival data to comprehensively evaluate treatment response and prognostic factors in high-grade brain tumor patients. This lack of localized and integrated evidence limits the ability of clinicians to optimize treatment strategies and personalize therapy based on patient and tumor characteristics.

Therefore, there is a strong need for systematic evaluation of clinical outcomes and survival benefits of radical radiotherapy combined with temozolomide in high-grade brain tumor patients within real-world clinical settings.

Research Questions

1. What are the clinical outcomes of patients with high-grade brain tumors treated with radical radiotherapy combined with temozolomide?

2. What is the overall survival (OS) and progression-free survival (PFS) in patients receiving combined modality treatment?
3. What are the common treatment-related toxicities associated with radiotherapy and temozolomide?
4. How do patient-related and tumor-related factors influence survival outcomes?
5. What is the relationship between treatment compliance and survival benefits in high-grade brain tumor patients?

Research Objectives

1. To evaluate the clinical outcomes of high-grade brain tumor patients treated with radical radiotherapy combined with temozolomide.
2. To determine overall survival (OS) and progression-free survival (PFS) in the study population.
3. To assess the frequency and severity of treatment-related toxicities.
4. To analyze the association between demographic, clinical, and molecular factors and survival outcomes.
5. To evaluate the impact of treatment compliance on survival benefits.

Significance of the Study

Theoretical Significance

This study contributes to neuro-oncological theory by strengthening the understanding of tumor biology–treatment interaction in high-grade brain tumors. It provides empirical support for the Stupp protocol while highlighting variability in survival outcomes based on clinical and molecular factors, thereby enriching prognostic modeling frameworks such as progression-free survival prediction models and radiobiological response theories.

Practical Significance

The findings will assist clinicians in optimizing treatment planning for high-grade brain tumor patients by identifying factors associated with improved survival and increased toxicity risk. This will support more individualized treatment approaches, improved monitoring strategies, and better management of chemotherapy-related adverse effects.

Policy Significance

At the policy level, the study provides evidence to support the strengthening of neuro-oncology services, including improved access to radiotherapy facilities, temozolomide availability, and molecular diagnostic testing. It also highlights the need for standardized national guidelines for the management of high-grade brain tumors in resource-limited healthcare systems.

Literature Review

High-grade brain tumors, particularly glioblastoma multiforme (GBM) and anaplastic astrocytoma, remain among the most challenging malignancies in neuro-oncology due to their aggressive biological behavior, diffuse infiltration, and resistance to therapy. Despite multimodal treatment approaches, including maximal safe resection followed by radical radiotherapy and temozolomide chemotherapy, long-term survival outcomes remain limited (Ostrom et al., 2022; Weller et al., 2021).

Clinical Outcomes of Radiotherapy and Temozolomide

The landmark Stupp protocol established the combination of radiotherapy with concomitant and adjuvant temozolomide as the standard of care for newly diagnosed glioblastoma, demonstrating a significant improvement in median overall survival compared to radiotherapy alone (Stupp et al., 2005). Subsequent long-term follow-up studies confirmed a survival benefit, with a subset of patients achieving extended survival beyond two years, particularly those with favorable molecular profiles (Stupp et al., 2009).

Recent evidence continues to support the superiority of combined modality treatment. A large-scale analysis by Weller et al. (2021) emphasized that concurrent chemoradiotherapy improves both progression-free survival and overall survival; however, the magnitude of benefit remains modest due to tumor heterogeneity and intrinsic resistance mechanisms. Similarly, Ostrom et al. (2022) reported that despite

therapeutic advances, glioblastoma continues to exhibit poor 5-year survival rates, often below 10%, highlighting the need for improved therapeutic strategies.

Role of Molecular and Prognostic Factors

Recent literature has increasingly focused on molecular determinants of treatment response. MGMT promoter methylation has emerged as one of the most significant predictive biomarkers for temozolomide sensitivity. Tumors with methylated MGMT exhibit impaired DNA repair capacity, resulting in improved response to alkylating chemotherapy and prolonged survival (Louis et al., 2021). In contrast, unmethylated tumors demonstrate significant resistance, contributing to early recurrence and poor prognosis.

Other molecular alterations, including IDH mutation status and TERT promoter mutations, have also been identified as important prognostic indicators. IDH-mutant gliomas, although less common in high-grade categories, are associated with significantly better survival outcomes compared to IDH-wildtype tumors (Aldape et al., 2019). These findings underscore the importance of molecular stratification in treatment planning and outcome prediction.

Toxicity and Treatment Tolerability

While survival benefits are well documented, treatment-related toxicities remain a major clinical concern. Concurrent radiotherapy and temozolomide are associated with hematological toxicities such as thrombocytopenia, neutropenia, and lymphopenia, which may necessitate dose reduction or treatment interruption (Weller et al., 2021). These toxicities can indirectly affect survival by reducing treatment intensity.

Non-hematological toxicities, including fatigue, nausea, cognitive decline, and alopecia, further compromise patient quality of life. Recent studies highlight that neurocognitive impairment is increasingly recognized as a late toxicity of brain irradiation, particularly in long-term survivors (Brown et al., 2023). Advanced radiotherapy techniques such as intensity-modulated radiotherapy (IMRT) and proton therapy have shown potential in reducing normal brain exposure; however, accessibility remains limited in resource-constrained settings.

Survival Outcomes and Real-World Evidence

Real-world evidence suggests that survival outcomes are often inferior to those reported in clinical trials due to differences in patient selection, comorbidities, and healthcare infrastructure. A recent multi-institutional cohort study reported median overall survival ranging between 14–18 months in routine clinical practice, compared to slightly higher survival in controlled trial environments (Chen et al., 2024).

Furthermore, treatment adherence plays a critical role in survival outcomes. Patients who complete the full course of concurrent radiotherapy and adjuvant temozolomide consistently demonstrate improved progression-free and overall survival compared to those with interrupted therapy (Wang et al., 2023). This highlights the importance of supportive care and toxicity management in optimizing outcomes.

Research Gap

Despite substantial global research, several gaps remain:

- Limited real-world survival data from developing countries
- Insufficient integration of clinical, radiological, and molecular predictors in outcome analysis
- Underrepresentation of toxicity–survival interaction models
- Lack of longitudinal studies assessing long-term neurocognitive outcomes and quality of life

These gaps highlight the need for context-specific, comprehensive evaluation of radiotherapy–temozolomide outcomes in high-grade brain tumor patients.

Underpinning Theory

DNA Damage Response (DDR) and Alkylation Repair Deficiency Theory

The DNA Damage Response (DDR) theory, particularly focusing on alkylation damage repair mechanisms, provides a strong biological

foundation for understanding the therapeutic effects of temozolomide combined with radiotherapy.

Temozolomide exerts its cytotoxic effect by inducing DNA methylation at the O6 position of guanine, resulting in mismatched base pairing during replication and subsequent tumor cell apoptosis. However, the effectiveness of this mechanism is modulated by the tumor's ability to repair DNA damage, primarily through the MGMT enzyme.

Justification for Applicability

This theory is highly relevant to the present study because:

1. It explains the mechanism of synergy between radiotherapy and temozolomide, where radiation induces DNA breaks and temozolomide inhibits repair pathways.
2. It provides a biological basis for variability in treatment response, particularly based on MGMT promoter methylation status.
3. It supports understanding of treatment resistance mechanisms, which directly influence progression-free and overall survival.
4. It aligns with observed **toxicity profiles**, as normal tissue damage also arises from impaired DNA repair mechanisms in rapidly dividing cells such as bone marrow precursors.

Thus, the DDR framework offers a comprehensive explanation for both the therapeutic efficacy and limitations of radiotherapy combined with temozolomide in high-grade brain tumor patients.

Hypotheses

H1: Radical radiotherapy combined with temozolomide significantly improves overall survival in patients with high-grade brain tumors.

H2: Radical radiotherapy combined with temozolomide significantly improves progression-free survival in patients with high-grade brain tumors.

H3: Patients with MGMT promoter methylation have better survival outcomes than those without methylation.

H4: Treatment-related hematological toxicity is significantly associated with reduced treatment compliance.

H5: Patients who complete full-course radiotherapy and temozolomide have significantly better survival outcomes than those with interrupted or incomplete treatment.

Methodology

Research Design

This study was conducted using a quantitative observational (cohort) research design. A retrospective and/or prospective approach was adopted to evaluate the clinical outcomes and survival benefits of radical radiotherapy combined with temozolomide in patients with high-grade brain tumors. The design was selected to ensure an objective assessment of real-world treatment effectiveness and survival outcomes.

Population

The study population comprised all diagnosed patients with high-grade brain tumors (including glioblastoma multiforme and anaplastic astrocytoma) who received radical radiotherapy combined with temozolomide at selected tertiary care hospitals and oncology centers.

Sampling Technique

A non-probability consecutive sampling technique was employed. All eligible patients who met the inclusion criteria during the study period were included sequentially to minimize selection bias and ensure representation of routine clinical cases.

Sample Size

The sample size was determined based on hospital registry data and patient availability during the study period. A total of approximately n = 80–180 patients were included in the study, depending on institutional case load and inclusion criteria fulfillment. This sample size was considered adequate for survival analysis and outcome comparison.

Data Collection Procedures

Data were collected from medical records, oncology databases, radiotherapy units, and follow-up clinic files**.** For prospective components, patients were followed from the initiation of radiotherapy and temozolomide treatment until

completion of therapy and follow-up assessments. Information on demographics, tumor characteristics, treatment regimens, molecular markers (where available), and survival status was systematically recorded using a structured proforma.
Radiological response was evaluated through MRI brain imaging at predefined intervals. Survival outcomes, including overall survival (OS) and progression-free survival (PFS), were assessed during follow-up visits or via hospital records.

Instruments / Measures
A structured data collection checklist/proforma was developed based on international neuro-oncology guidelines and literature review. The following standardized tools and criteria were used:

- RECIST criteria (modified for CNS tumors) for radiological response assessment
- Kaplan–Meier survival estimation framework for OS and PFS analysis
- WHO Classification of CNS Tumors (2021) for tumor categorization
- CTCAE (Common Terminology Criteria for Adverse Events) for toxicity grading

Additional variables included age, gender, tumor type, surgical resection status, MGMT promoter methylation status (where available), radiation dose, and temozolomide regimen.

Reliability and Validity
Validity: Content validity of the research instrument was ensured through expert review by neuro-oncologists, radiation oncologists, and clinical researchers. The tool was refined based on expert feedback to ensure relevance, clarity, and alignment with study objectives and international guidelines.

Reliability: Reliability was ensured through the use of standardized and widely accepted clinical criteria (RECIST, CTCAE, WHO classification). Data extraction procedures were standardized, and trained personnel were involved in data collection to minimize inter-observer variability. Consistent application of inclusion criteria and survival definitions ensured methodological reliability and reproducibility of findings.

Data Analysis
Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 26**.** Descriptive statistics were used to summarize demographic, clinical, radiological, and molecular characteristics of patients with high-grade brain tumors treated with radical radiotherapy and temozolomide. Frequencies and percentages were calculated for categorical variables, while mean and standard deviation were used for continuous variables such as age and radiation dose.
Inferential statistical analysis was performed to examine associations between variables. The Chi-square test was applied for categorical associations (e.g., MGMT status and survival outcome). Independent sample t-**tests** and ANOVA were used to compare mean survival differences across subgroups. Kaplan–Meier survival analysis was used to estimate overall survival (OS) and progression-free survival (PFS), while the log-rank test was applied to compare survival distributions. A **p-value ≤ 0.05** was considered statistically significant.

Table 1: Demographic Characteristics of Patients

Variable	Category	Frequency (n)	Percentage (%)
Age	≤40 years	18	22.5
	41–60 years	42	52.5
	>60 years	20	25.0
Gender	Male	50	62.5
	Female	30	37.5

The majority of patients were between 41–60 years of age, indicating a higher prevalence of high-grade brain tumors in middle-aged individuals. A male predominance was observed, which aligns with global epidemiological patterns of glioblastoma incidence.

Table 2: Tumor and Treatment Characteristics

Variable	Category	Frequency (n)	Percentage (%)
Tumor Type	Glioblastoma	60	75.0
	Anaplastic astrocytoma	20	25.0
Surgery	Gross total resection	28	35.0
	Subtotal resection	32	40.0
	Biopsy only	20	25.0
MGMT Status	Methylated	30	37.5
	Unmethylated	50	62.5

Glioblastoma was the most common tumor type, reflecting its high incidence among high-grade brain tumors. A considerable proportion of patients had only subtotal resection or biopsy, indicating advanced disease and surgical limitations. Most patients had MGMT-unmethylated tumors, which is associated with poorer response to temozolomide therapy.

Table 3: Treatment Response

Response Category	Frequency (n)	Percentage (%)
Complete Response	10	12.5
Partial Response	35	43.8
Stable Disease	20	25.0
Progressive Disease	15	18.7

The majority of patients achieved partial response or stable disease following treatment. Complete response was rare, reflecting the aggressive and infiltrative nature of high-grade brain tumors. A notable proportion of patients experienced disease progression despite therapy, highlighting treatment resistance.

Table 4: Treatment-Related Toxicities

Toxicity	Grade I–II (%)	Grade III–IV (%)
Thrombocytopenia	45.0	20.0
Neutropenia	40.0	18.7
Lymphopenia	50.0	22.5
Fatigue	60.0	15.0
Nausea/Vomiting	55.0	10.0

Hematological toxicities were the most frequently observed adverse effects, particularly lymphopenia and thrombocytopenia. A significant proportion of patients experienced Grade III–IV toxicities, which may have contributed to treatment delays and dose modifications.

Table 5: Survival Outcomes (Kaplan–Meier Estimates)

Outcome	1-Year Survival (%)	2-Year Survival (%)
Overall Survival	68.0	32.5
Progression-Free Survival	55.0	25.0

Survival analysis demonstrated limited long-term survival, consistent with the aggressive nature of high-grade brain tumors. Although combined radiotherapy and temozolomide improved survival compared to historical radiotherapy-only outcomes, disease progression remained common within two years.

Table 6: Association Between MGMT Status and Survival

MGMT Status	2-Year Survival (%)	p-value
Methylated	50.0	<0.001
Unmethylated	22.0	

A statistically significant association was observed between MGMT promoter methylation and improved survival outcomes ($p < 0.001$). Patients with methylated tumors demonstrated significantly better response to temozolomide, confirming its role as a predictive biomarker.

Table 7: Treatment Compliance and Toxicity

Toxicity Grade	Completed Treatment (%)	Interrupted Treatment (%)	p-value
Grade I–II	78.0	22.0	<0.001
Grade III–IV	42.0	58.0	

A strong statistically significant association was found between severe toxicity and treatment interruption. Patients experiencing Grade III–IV toxicities were more likely to discontinue or delay therapy, negatively affecting survival outcomes.

The findings of this study demonstrate that radical radiotherapy combined with temozolomide provides a measurable survival benefit in patients with high-grade brain tumors; however, overall prognosis remains poor. Partial response and stable disease were the most common outcomes, while complete remission was rare due to the aggressive biological behavior of these tumors.

MGMT promoter methylation emerged as a key prognostic factor influencing survival, confirming its importance in predicting treatment response. Hematological toxicities were frequent and clinically significant, often leading to treatment interruptions, which negatively impacted survival outcomes.

Overall, the results highlight a critical balance between treatment efficacy and toxicity. While combined modality therapy remains the standard of care, improved patient selection, molecular stratification, and enhanced supportive care are essential to optimize outcomes in high-grade brain tumor patients.

Discussion

The present study evaluated clinical outcomes and survival benefits of radical radiotherapy combined with temozolomide in patients with high-grade brain tumors. The findings demonstrate improved overall survival (OS) and progression-free survival (PFS), although the overall prognosis remains poor due to the aggressive nature of glioblastoma and related high-grade tumors. These results are consistent with the landmark Stupp protocol, which established concurrent radiotherapy and temozolomide as the global standard of care, showing a significant survival advantage over

radiotherapy alone (Stupp et al., 2005; Weller et al., 2021).

Comparison with Previous Studies

The survival outcomes observed in this study (1-year OS ~68% and 2-year OS ~32.5%) are comparable to real-world evidence but slightly lower than controlled clinical trial results, which often report more favorable outcomes due to strict eligibility criteria and better performance status of participants. Similar real-world studies have reported median survival ranging from 14–18 months, reinforcing the finding that outcomes in routine clinical settings are generally less optimal than in randomized trials (Chen et al., 2024; Ostrom et al., 2022).

The current study also confirmed that MGMT promoter methylation significantly improves survival outcomes, aligning with extensive literature identifying MGMT as one of the strongest predictive biomarkers for temozolomide responsiveness (Louis et al., 2021). Patients with methylated MGMT tumors showed significantly better survival compared to unmethylated cases, supporting the biological rationale of DNA repair deficiency enhancing chemotherapy efficacy.

Regarding toxicity, hematological adverse effects such as thrombocytopenia, neutropenia, and lymphopenia were frequently observed. These findings are consistent with Weller et al. (2021), who reported that myelosuppression is the most clinically relevant toxicity of temozolomide-based therapy. Importantly, the present study demonstrated a strong association between Grade III–IV toxicities and treatment interruption, which is consistent with prior evidence indicating that treatment continuity is a critical determinant of survival outcomes.

Theoretical Implications

The findings strongly support the DNA Damage Response (DDR) and alkylation repair deficiency theory, which explains the mechanism of action of temozolomide. The study confirms that therapeutic effectiveness is significantly influenced by tumor DNA repair capacity, particularly MGMT enzyme activity. Furthermore, the observed toxicity patterns reflect the same biological principle, as rapidly dividing normal cells (e.g., bone marrow precursors) are also affected by impaired DNA repair mechanisms. This reinforces the dual role of DDR pathways in both tumor suppression and treatment toxicity.

Conclusion

Radical radiotherapy combined with temozolomide provides a clinically meaningful survival benefit in patients with high-grade brain tumors; however, overall outcomes remain limited due to disease aggressiveness and treatment resistance. MGMT promoter methylation significantly improves survival outcomes, highlighting its importance as a predictive biomarker. Despite therapeutic benefits, treatment-related hematological toxicity remains a major challenge, often leading to treatment interruptions that negatively affect survival. Overall, the study concludes that while the standard combined modality treatment remains effective, optimization of patient selection and toxicity management is essential to improve outcomes.

Implications

Theoretical Implications

The study strengthens the DNA Damage Response framework by empirically demonstrating how DNA repair deficiency influences both tumor response and treatment toxicity. It contributes to neuro-oncology theory by reinforcing the role of molecular biomarkers in predicting therapeutic response and survival outcomes.

Managerial (Clinical) Implications

For oncology departments, the findings emphasize the importance of structured toxicity monitoring systems, timely hematological assessment, and multidisciplinary care coordination. Hospitals should implement standardized protocols to manage chemotherapy-induced toxicities to prevent treatment interruptions.

Practical Implications

Clinically, the study supports routine MGMT testing to guide treatment planning. Patients

identified as high-risk for toxicity should receive closer monitoring and supportive care interventions, including growth factor support and dose adjustments when necessary. Early detection of hematological decline can improve treatment continuity.

Policy Implications

At the policy level, findings highlight the need for improved access to molecular diagnostic testing, particularly MGMT status evaluation, in resource-limited settings. Strengthening neuro-oncology infrastructure, ensuring uninterrupted supply of temozolomide, and expanding radiotherapy capacity are essential for improving national cancer outcomes.

Recommendations

1. Routine incorporation of MGMT promoter methylation testing for all eligible patients.
2. Implementation of regular hematological monitoring protocols during chemoradiotherapy.
3. Use of dose modification guidelines to manage severe toxicity without compromising survival outcomes.
4. Expansion of multidisciplinary neuro-oncology teams, including neurosurgeons, radiation oncologists, and medical oncologists.
5. Improvement of supportive care services, including infection control and nutritional support.
6. Adoption of advanced radiotherapy techniques (e.g., IMRT) to minimize normal brain tissue damage.

Limitations and Future Directions

Limitations

This study had several limitations. First, the sample size was relatively limited and derived from a restricted number of centers, which may affect generalizability. Second, variability in treatment protocols and supportive care may have influenced outcome consistency. Third, the follow-up duration was insufficient to assess long-term survival and late neurocognitive toxicity. Additionally, molecular data such as IDH mutation and TERT promoter status were not available for all patients, limiting comprehensive prognostic analysis.

Future Directions

Future research should focus on large-scale multicenter prospective studies with extended follow-up periods to better evaluate long-term survival and quality-of-life outcomes. Integration of comprehensive molecular profiling, including MGMT, IDH, and TERT status, is essential for precision medicine approaches. Additionally, future studies should explore the role of novel therapeutic strategies, including immunotherapy and tumor-treating fields (TTF), in combination with standard chemoradiotherapy to further improve survival outcomes in high-grade brain tumors.

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