Radioresistant meningioma

- Establishment and transcriptomic characteristics of radio-resistant meningioma cell lines
- KEAP1-mutant atypical meningioma: illustrative case
- Noncoding RNA landscape and their emerging roles as biomarkers and therapeutic targets in meningioma
- Non-coding RNAs as Genetic Biomarkers for the Diagnosis, Prognosis, Radiosensitivity, and Histopathologic Grade of Meningioma
- Necrosis and Brain Invasion Predict Radio-Resistance and Tumor Recurrence in Atypical Meningioma: A Retrospective Cohort Study
- Differentially Expressed MicroRNAs in Radioresistant and Radiosensitive Atypical Meningioma: A Clinical Study in Chinese Patients
- First proton minibeam radiation therapy treatment plan evaluation
- Does Proton Therapy Have a Future in CNS Tumors?

Meningiomas are generally considered **radiation-sensitive tumors**, but some cases exhibit **radioresistance**, leading to treatment failure or recurrence after radiotherapy. This is particularly relevant for **atypical (WHO grade II) and anaplastic (WHO grade III) meningiomas**, which have higher recurrence rates and resistance to conventional treatments.

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1. Causes of Radio-resistance in Meningiomas Several mechanisms may contribute to radio-resistance in meningiomas:

A. Tumor Grade and Molecular Profile - **Benign meningiomas (WHO I)**: Typically radiosensitive. - **Atypical (WHO II) & Anaplastic (WHO III) meningiomas**: More aggressive and resistant to radiation. - **Mutations and genetic alterations**:

1. **TERT promoter mutations** → Associated with aggressive behavior and radio-resistance.
2. **CDKN2A/B deletions** → Linked to higher recurrence rates.
3. **NF2 mutations** → Found in many meningiomas but not necessarily linked to radio-resistance.

B. Hypoxia-Induced Resistance - Tumor hypoxia reduces radiation effectiveness by limiting **reactive oxygen species (ROS) production**, which is crucial for radiation-induced DNA damage. - Some meningiomas, especially large or recurrent ones, may have **hypoxic regions**, leading to decreased radiosensitivity.

C. Enhanced DNA Repair Mechanisms - Meningiomas may **upregulate DNA repair pathways** such as:

1. **Non-homologous end joining (NHEJ)**
2. **Homologous recombination (HR)**

- This allows cells to recover from radiation-induced damage more effectively.

D. Cell Cycle Alterations - Tumor cells in **G0 or S-phase** are more radio-resistant compared to those in **G2/M-phase**, where radiation is more effective.

E. Tumor Microenvironment Factors - **Immune evasion**: Some high-grade meningiomas exhibit **immune-suppressive microenvironments**, reducing the immune-mediated effects of

radiation. - **Inflammation & angiogenesis**: Overexpression of VEGF (vascular endothelial growth factor) may contribute to resistance.

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2. Management Strategies for Radio-resistant Meningioma #### **A. Optimized Radiation Therapy Approaches** 1. **Stereotactic Radiosurgery (SRS) or Hypofractionated Stereotactic Radiotherapy (HSRT)**

1. High precision with fewer fractions can **overcome resistance** by delivering **higher biological effective doses (BED)**.
2. Recommended for **small residual or recurrent tumors**.

2. **Dose Escalation Strategies**

1. Higher doses (e.g., >60 Gy) may improve control in **atypical/anaplastic meningiomas**, but toxicity must be considered.
2. Proton therapy is sometimes used to **maximize dose delivery** while minimizing surrounding tissue damage.

3. **Re-irradiation in Recurrent Cases**

1. Selected patients may benefit from **a second course of radiotherapy** after recurrence.
2. Fractionated re-irradiation can be considered, balancing efficacy with toxicity.

B. Radiosensitizers & Combination Therapies 1. **Targeting DNA Repair Pathways**

1. **PARP inhibitors (e.g., olaparib)**: May sensitize tumors by impairing DNA repair.
2. **ATM/ATR inhibitors**: Target key radiation response pathways.

2. **Hypoxia Modulation**

1. **Hypoxia-activated prodrugs (e.g., tirapazamine)** or **hyperbaric oxygen therapy** may increase radiosensitivity.

3. **VEGF & Angiogenesis Inhibitors**

1. **Bevacizumab (anti-VEGF antibody)**: May reduce radio-resistance by normalizing blood flow and improving oxygenation.

4. **Immunotherapy + Radiation**

1. **Immune checkpoint inhibitors (e.g., pembrolizumab, nivolumab)** are being explored in combination with radiotherapy for high-grade meningiomas.

C. Systemic Therapy for Refractory Cases - **Somatostatin receptor analogs (e.g., octreotide)** - **Targeted therapies (e.g., mTOR inhibitors, tyrosine kinase inhibitors)** for NF2-mutated tumors - **Hormonal therapy** (progestin antagonists) in selected cases

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3. Future Directions & Research - **Molecular profiling** of meningiomas may allow for **personalized radiation therapy**. - Ongoing trials are investigating **novel radiosensitizers and immunotherapeutic combinations**. - **Liquid biopsies and circulating tumor DNA (ctDNA)**

could help predict radiation response.

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Conclusion Radio-resistant meningiomas, especially **WHO II and III tumors**, remain a therapeutic challenge. Advances in **stereotactic radiotherapy, radiosensitizers, and targeted therapies** offer hope for improving outcomes. A **multimodal approach**, including molecular characterization, may help overcome resistance in recurrent or high-grade cases.

Preclinical experimental study with molecular and transcriptomic analysis

A study aimed to establish radio-resistant meningioma cell lines and uncover molecular mechanisms driving radioresistance to identify potential biomarkers and therapeutic targets.

Radio-resistant meningioma cell lines (IOMM-Lee-RR, CH157-RR) were developed using a progressive radiation dose (cumulative 90 Gy). Cell morphology, radiosensitivity, apoptosis, viability, migration, invasion, cell cycle, and DNA damage repair were analyzed via clonogenic assays, flow cytometry, and Western blotting. Transcriptome sequencing was performed to identify differentially expressed genes (DEGs), followed by KEGG and GO enrichment analyses. Protein-protein interaction (PPI) analysis was conducted to identify hub genes. TK1 expression was further validated in a cohort of 350 meningiomas and the GSE189672 dataset.

Radio-resistant meningioma cell lines exhibited enhanced survival, reduced apoptosis, increased cell viability, and superior migratory and invasive abilities compared to parental cells. Under radiation, these cells showed G0/G1 phase accumulation and reduced G2/M phase arrest, along with enhanced DNA repair capacity, as evidenced by lower γ-H2AX expression and fewer DNA damage foci. Transcriptome analysis revealed significant enrichment in metabolic pathways, DNA repair, and cell cycle regulation. Among 34 hub genes identified, TK1 emerged as a key gene, being highly expressed in recurrent and high-grade meningiomas and positively correlated with Ki67. Analysis of the GSE189672 dataset confirmed TK1 as a poor prognostic factor associated with tumor recurrence.

Radio-resistant meningioma cells exhibit enhanced DNA repair, migration, invasion, and altered cell cycle dynamics. Thymidine kinase 1 was identified as a promising biomarker and therapeutic target for overcoming radio-resistance in meningiomas [1)]

1)
Yu J, Ren L, Wu T, Hua L, Wang D, Wang Y, Xie Q, Deng J, Gong Y. Establishment and transcriptomic characteristics of radio-resistant meningioma cell lines. J Neurooncol. 2025 Feb 28. doi: 10.1007/s11060-025-04966-6. Epub ahead of print. PMID: 40019713.