Topic #2: Electromagnetic Waves to Treat Glioblastomas

MEDSCIEN 9508

Dr. Arthur Brown

February 21, 2025

Interdisciplinary Medical Sciences

Schulich School of Medicine and Dentistry

Western University

**Assignment Acknowledgement**

No AI was used to generate the contents of paper.

**Author Contributions**

|  |  |  |
| --- | --- | --- |
| **Student Name** | **Student Number** | **Contributions** |
| Cassandra Fraser | 251093944 | #1, Reviewed and Edited other group member’s parts |
| Rishika Sharma | 251008648 | Create Google Doc, #2, general formatting, overall editing |
| Preston McCabe | 251111362 | #3, overall final review, and citation help. |
| Sarah Catania | 251159410 | #4, citations, reviewed other group members’ parts |

1. **The Problem/Need**

**Glioblastoma Multiforme (GBM)**

Glioblastoma multiforme (GBM) is the most malignant and invasive form of glioma, posing significant challenges in both patient prognosis and treatment.[1](https://www.zotero.org/google-docs/?KzRdTf) Gliomas originate from glial cells such as oligodendrogliomas, astrocytomas, and ependymoma, accounting for approximately 80% of all malignant central nervous system (CNS) tumours.[2](https://www.zotero.org/google-docs/?bahpSk) Among these, GBM is the most prevalent, accounting to 45.2% of primary malignant brain and CNS tumours.[1](https://www.zotero.org/google-docs/?xb11Hm)

**The Problem**

Despite extensive research efforts, therapeutic advancements have failed to produce substantial improvements in patient lifespans. A major barrier in GBM treatment is the inability of many therapeutic agents to effectively penetrate the blood-brain barrier (BBB) and achieve sufficient concentrations within the CNS.[3](https://www.zotero.org/google-docs/?CV1tKl) Additional challenges are due to the tumour’s invasive nature, genetic heterogeneity, and treatment resistance. Therefore, diseases of the CNS are among the most difficult to treat.[4](https://www.zotero.org/google-docs/?mxlDw9) Existing treatments often lead to systemic toxicity and limited therapeutic efficacy.[2](https://www.zotero.org/google-docs/?SCmNdT) As a result of GBM and the treatment challenges, patient survival rates have not significantly improved, emphasizing the need for novel treatment strategies.

**The Need**

Current treatment strategies, including surgery, chemotherapy, and radiation, are often insufficient in preventing tumour recurrence, due to GBM’s highly invasive and resistant nature. Additionally, while electrotherapeutic therapies have been observed to have antitumor impacts on various cancer types, their application remains limited by their inability to selectively target tumour cells without affecting healthy tissue.[5](https://www.zotero.org/google-docs/?G0FDCs) A more advanced therapeutic approach is required to address these challenges by ensuring precise tumour targeting, minimizing systemic toxicity, and improving treatment efficacy. Advancing GBM treatment through innovative approaches is essential to enhance clinical outcomes.

1. **The Possible Solution**

Electrotherapeutics have been observed to have anti-tumour impacts on various cancer types *in vivo* and *in vitro*.[6,7](https://www.zotero.org/google-docs/?bgv2Hi) The underlying mechanism of these therapies is rooted in the differing frequency and intensity of delivered electrical pulses.[8](https://www.zotero.org/google-docs/?CjjsA6) Traditional electroporation utilizes high-voltage pulses to create temporary pores in the cell membrane, leading to drug uptake.[9](https://www.zotero.org/google-docs/?Qfle18) However, alternating electric fields (AEFs) function at intermediate frequencies, disrupting tumour mitosis without directly damaging the cell.[10](https://www.zotero.org/google-docs/?IcLnQ3) Intratumoral Modulation Therapy (IMT) is a minimally invasive, implantable electrotherapy solution that provides alternating electric fields straight into the site of the tumour thereby inducing tumour cell apoptosis.[10](https://www.zotero.org/google-docs/?zeQvwi)

**The Technology**

IMT is an electrotherapeutic treatment that leverages high-frequency electric stimulation to disrupt tumour cell mitosis while maintaining normal brain function.[5](https://www.zotero.org/google-docs/?GlKyEM) IMT uses sustained low-intensity stimulation to selectively dismantle mitotic spindle formation in rapidly dividing GBM cells.[11](https://www.zotero.org/google-docs/?H4jAwF) The intervention requires the surgical implantation of a cannula-electrode placed directly within the tumour, which is most probably in the caudate putamen region.[10](https://www.zotero.org/google-docs/?v9DySq) The precise electrode placement continuously delivers electrical pulses directly to the tumour resulting in maximum efficacy.[5](https://www.zotero.org/google-docs/?vCTQF7) Post implantation the electrode is connected to a waveform generator that creates alternating electric fields at a frequency that selectively causes cytotoxic impacts on GBMS cells.[5](https://www.zotero.org/google-docs/?hOFP6p) Such electric fields dismantle intracellular organization specifically targeting the alignment of microtubules. This level of disruption results in mitotic arrest and eventually tumour cell apoptosis.[10](https://www.zotero.org/google-docs/?IXCEN5)

An advantage of using the IMT model over other GBM therapies is that its efficacy is not limited by the blood-brain barrier, as seen with chemotherapy agents which leads to limited bioavailability.[12](https://www.zotero.org/google-docs/?NhKdlc) Through targeting electrical pulses at the tumour site malignant cells are maximally exposed to the therapy.[5](https://www.zotero.org/google-docs/?cneHSM) Additionally, the therapy is selective for the tumour cells, whereas traditional therapies are indiscriminate towards cancer and healthy cells.

1. **The Customer/Market**

**Market Summary**

IMT use for GBM represents a heterogeneous market with two major stakeholders and massive size potential. Firstly, there are the patients, GBM is the most common malignant primary brain tumour and has shown a stark increase in incidence. In the United States alone they have seen an incidence increase from 0.73 per 100,000 in 2008 to 4.49 per 100,000 in 2017.[13](https://www.zotero.org/google-docs/?BbaqRM) This places current estimates that every year more than 15,000 North Americans will receive a diagnosis of GBM, and on a global scale this can be extrapolated to 280,000 new cases per year globally.[14](https://www.zotero.org/google-docs/?0RieMk) Because GBM has an extremely high mortality rate, with the median survival time often being a year or less at time of diagnosis, the total number of those living with GBM is closely related to the rate of incidence.[15](https://www.zotero.org/google-docs/?mGs7PY) However, this indicates that with increases in survival of those diagnosed with GBM, the total number of those living with these tumours will increase greatly with an improved prognosis that IMT enables with preclinical evidence of significantly attenuating tumour growth.[5](https://www.zotero.org/google-docs/?OSiPfT) Furthermore if the efficacy of IMT can be established for these incredibly aggressive brain tumours, it can then expand into the market of other solid tumour cancers, with the potential international market in excess of 10 million people every year receiving a cancer diagnosis who could potentially benefit greatly from the use of IMT.[16](https://www.zotero.org/google-docs/?7Q54h8)

Secondly, IMT offers massive savings for insurance providers as the increased survivability and longevity permitted from IMT has significant potential healthcare savings. A study looking at insurance claims for high grade gliomas in Rochester, New York found that the highest median costs associated with patient treatment were outpatient radiology $46,294.91 followed by inpatient surgery $30,786.47.[17](https://www.zotero.org/google-docs/?qzfvig) In the context that following resection surgery 9 out of 10 of the tumours will return means that GBMs incur a massive cost to intervene, especially considering the cost, time, and resource intensity of resection surgery. Looking at these insurance claims researchers also found that maintenance care at $14,490.53 was minimal compared to initial and recurrence treatment being $66,673.80 and $52,125.77 respectively.[17](https://www.zotero.org/google-docs/?Hmoz5g) IMT helps by increasing the efficacy of maintenance treatment, and decreasing the likelihood of recurrence treatment, saving money and precious operating room time.[18](https://www.zotero.org/google-docs/?L3tJcA) To this end, the cost saving potential of IMT for the 88 patient’s insurance claims analyzed between 2011 and 2017 could have represented over $4.5 million in savings along with improved patient prognosis.

1. **The Value Proposition**

**What is the Value Proposition?**

IMT was developed to deliver targeted electrical stimulation to GBM-affected brain regions. A study at Western University tested IMT on a rat model of GBM, demonstrating that the technology successfully attenuated tumour growth.[5](https://www.zotero.org/google-docs/?WHijbi) These findings suggest that IMT could provide similar benefits in human patients, addressing a critical need in GBM treatment.

Current treatment options for GBM- chemotherapy (e.g. temozolomide), radiation, and surgical resection- offer limited success due to the aggressive nature of the tumour.[19](https://www.zotero.org/google-docs/?sxvgXV) Despite these treatments, the median survival after diagnosis remains only 12-15 months.[19](https://www.zotero.org/google-docs/?aMSYpp) Existing therapies face major limitations, such as chemotherapy struggles to cross the blood-brain barrier, and 90% of surgically removed tumours regrow.[5,20](https://www.zotero.org/google-docs/?E6gaUe) Alternative electrotherapies, such as electroporation, have been explored but lack specificity, damaging both cancerous and healthy cells.[9](https://www.zotero.org/google-docs/?kjnqN4)

IMT addresses these gaps by using AEFs, which have demonstrated tumour growth inhibition, size reduction, and enhanced effectiveness when combined with chemotherapy.[11,21](https://www.zotero.org/google-docs/?ZxQQrD) Unlike external AEF therapies, which require patients to wear a device and maintain a shaved head, IMT is fully implantable. This design not only enhances patient compliance but also reduces stigma and lifestyle disruption[5](https://www.zotero.org/google-docs/?d6Mklj) External AEF therapy demands 18 hours of daily use for significant survival benefits, yet studies have reported a 20% discontinuation rate due to non-compliance.[22](https://www.zotero.org/google-docs/?BHED5p) IMT’s implantable nature eliminates this burden, providing continuous, targeted treatment with minimal interference in daily life. Additionally, AEF therapy has been shown to produce fewer side effects compared to chemotherapy, which often causes nausea, vomiting, fatigue, and pain.[22,23](https://www.zotero.org/google-docs/?nWNngm) Studies have also shown quality of life improvements such as improved cognition.[22](https://www.zotero.org/google-docs/?rPcj5o) By reducing both the physician and cognitive burden of cancer treatment, IMT represents a significant improvement in patient care while maintaining effectiveness.

**Why does the Customer want to Adopt the New Technology?**

Beyond improving patient outcomes, IMT presents valuable opportunities for investors and physicians. If successful in GBM, this technology could be expanded to treat other cancers, significantly broadening its market potential.[5,24](https://www.zotero.org/google-docs/?wKmPBu) For investors, this scalability translates into greater commercial viability, while for physicians, it offers a promising tool to enhance treatment efficacy and patient quality of life across multiple cancer types.

Overall, IMT offers a transformative approach to GBM treatment by overcoming the limitations of current therapies. Its implantable nature provides a more direct and continuous treatment, improving both efficacy and patient adherence while reducing the side effects associated with traditional therapies. Beyond its immediate application in GBM, IMT has the potential to expand into other cancer treatments, presenting an opportunity for investors and a promising advancement for physicians. By enhancing survival rates, improving quality of life, and minimizing treatment-related burdens, IMT stands as a valuable innovation in the fight against aggressive cancers.

**References:**

[1. Kanderi T, Munakomi S, Gupta V. Glioblastoma Multiforme. In: *StatPearls*. StatPearls Publishing; 2025. Accessed February 21, 2025.](https://www.zotero.org/google-docs/?zzjVRP) <http://www.ncbi.nlm.nih.gov/books/NBK558954/>

[2. Agnihotri S, Burrell KE, Wolf A, et al. Glioblastoma, a brief review of history, molecular genetics, animal models and novel therapeutic strategies. *Arch Immunol Ther Exp (Warsz)*. 2013;61(1):25-41. doi:10.1007/s00005-012-0203-0](https://www.zotero.org/google-docs/?zzjVRP)

[3. Mohs RC, Greig NH. Drug discovery and development: Role of basic biological research. *Alzheimers Dement (N Y)*. 2017;3(4):651-657. doi:10.1016/j.trci.2017.10.005](https://www.zotero.org/google-docs/?zzjVRP)

[4. Banks WA, Rhea EM, Reed MJ, Erickson MA. The penetration of therapeutics across the blood-brain barrier: Classic case studies and clinical implications. *Cell Rep Med*. 2024;5(11):101760. doi:10.1016/j.xcrm.2024.101760](https://www.zotero.org/google-docs/?zzjVRP)

[5. Cooper M. Establishing an In Vivo Model for Intratumoral Modulation Therapy for Glioblastoma Multiforme. *Electronic Thesis and Dissertation Repository*. Published online June 27, 2016. https://ir.lib.uwo.ca/etd/3814](https://www.zotero.org/google-docs/?zzjVRP)

[6. Neal RE, Rossmeisl JH, D’Alfonso V, et al. In Vitro and Numerical Support for Combinatorial Irreversible Electroporation and Electrochemotherapy Glioma Treatment. *Ann Biomed Eng*. 2014;42(3):475-487. doi:10.1007/s10439-013-0923-2](https://www.zotero.org/google-docs/?zzjVRP)

[7. In Vivo Evidences of Nanosecond Pulsed Electric Fields for Melanoma Malignancy Treatment on Tumor-Bearing BALB/c Nude Mice - Fei Guo, Chenguo Yao, Chengxiang Li, Yan Mi, Qiao Peng, Junying Tang, 2014. Accessed February 21, 2025.](https://www.zotero.org/google-docs/?zzjVRP) <https://journals.sagepub.com/doi/10.7785/tcrt.2012.500385>

[8. Controlling Cell Behavior Electrically: Current Views and Future Potential | Physiological Reviews | American Physiological Society. Accessed February 21, 2025.](https://www.zotero.org/google-docs/?zzjVRP) <https://journals.physiology.org/doi/full/10.1152/physrev.00020.2004>

[9. Gehl J. Electroporation: theory and methods, perspectives for drug delivery, gene therapy and research. *Acta Physiol Scand*. 2003;177(4):437-447. doi:10.1046/j.1365-201X.2003.01093.x](https://www.zotero.org/google-docs/?zzjVRP)

[10. Giladi M, Schneiderman RS, Voloshin T, et al. Mitotic Spindle Disruption by Alternating Electric Fields Leads to Improper Chromosome Segregation and Mitotic Catastrophe in Cancer Cells. *Sci Rep*. 2015;5(1):18046. doi:10.1038/srep18046](https://www.zotero.org/google-docs/?zzjVRP)

[11. Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors | PNAS. Accessed February 21, 2025.](https://www.zotero.org/google-docs/?zzjVRP) <https://www.pnas.org/doi/10.1073/pnas.0702916104>

[12. Pancreatic adenocarcinoma | European Radiology. Accessed February 21, 2025.](https://www.zotero.org/google-docs/?zzjVRP) <https://link.springer.com/article/10.1007/s00330-006-0435-7>

[13. Grech N, Dalli T, Mizzi S, Meilak L, Calleja N, Zrinzo A. Rising Incidence of Glioblastoma Multiforme in a Well-Defined Population. *Cureus*. 12(5):e8195. doi:10.7759/cureus.8195](https://www.zotero.org/google-docs/?zzjVRP)

[14. Grochans S, Cybulska AM, Simińska D, et al. Epidemiology of Glioblastoma Multiforme–Literature Review. *Cancers*. 2022;14(10):2412. doi:10.3390/cancers14102412](https://www.zotero.org/google-docs/?zzjVRP)

[15. Brown NF, Ottaviani D, Tazare J, et al. Survival Outcomes and Prognostic Factors in Glioblastoma. *Cancers*. 2022;14(13):3161. doi:10.3390/cancers14133161](https://www.zotero.org/google-docs/?zzjVRP)

[16. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*. 2024;74(3):229-263. doi:10.3322/caac.21834](https://www.zotero.org/google-docs/?zzjVRP)

[17. Liu Y, Tyler E, Lustick M, Klein D, Walter KA. Healthcare Costs for High-grade Glioma. *Anticancer Research*. 2019;39(3):1375-1381. doi:10.21873/anticanres.13251](https://www.zotero.org/google-docs/?zzjVRP)

[18. Wu W, Klockow JL, Zhang M, et al. Glioblastoma Multiforme (GBM): An overview of current therapies and mechanisms of resistance. *Pharmacol Res*. 2021;171:105780. doi:10.1016/j.phrs.2021.105780](https://www.zotero.org/google-docs/?zzjVRP)

[19. Stupp R, Mason WP, Bent MJ van den, et al. Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. *New England Journal of Medicine*. 2005;352(10):987-996. doi:10.1056/NEJMoa043330](https://www.zotero.org/google-docs/?zzjVRP)

[20. Berens ME, Giese A. “...those left behind.” Biology and Oncology of Invasive Glioma Cells. *Neoplasia*. 1999;1(3):208-219. doi:10.1038/sj.neo.7900034](https://www.zotero.org/google-docs/?zzjVRP)

[21. Di Sebastiano AR, Deweyert A, Benoit S, et al. Preclinical outcomes of Intratumoral Modulation Therapy for glioblastoma. *Sci Rep*. 2018;8(1):7301. doi:10.1038/s41598-018-25639-7](https://www.zotero.org/google-docs/?zzjVRP)

[22. Stupp R, Wong ET, Kanner AA, et al. NovoTTF-100A versus physician’s choice chemotherapy in recurrent glioblastoma: A randomised phase III trial of a novel treatment modality. *European Journal of Cancer*. 2012;48(14):2192-2202. doi:10.1016/j.ejca.2012.04.011](https://www.zotero.org/google-docs/?zzjVRP)

[23. An Evidence-Based Review of Alternating Electric Fields Therapy for Malignant Gliomas | Current Treatment Options in Oncology. Accessed February 21, 2025.](https://www.zotero.org/google-docs/?zzjVRP) <https://link.springer.com/article/10.1007/s11864-015-0353-5>

[24. Anti-cancer mechanisms of action of therapeutic alternating electric fields (tumor treating fields [TTFields]) | Journal of Molecular Cell Biology | Oxford Academic. Accessed February 21, 2025. https://academic.oup.com/jmcb/article/14/8/mjac047/6668799](https://www.zotero.org/google-docs/?zzjVRP)