



Tumor Treating Fields for Glioblastoma Multiforme: Effectiveness and Safety

Sıtkı Utku AKAY,¹ Oğuzhan KESEN²

¹Department of Radiation Oncology, Muğla Training and Research Hospital, Muğla-Türkiye

²Department of Medical Oncology, Rize Recep Tayyip Erdoğan University, Rize-Türkiye

SUMMARY

Glioblastoma multiforme (GBM) is the most common and most lethal primary brain tumor in adults. The standard treatment for GBM with good performance is maximal surgical resection followed by adjuvant chemoradiotherapy and adjuvant temozolomide therapy. In addition to this treatment, alternating electric fields or tumor treating fields (TTFields) are also recommended at category 1 level in the NCCN guidelines. In this review, the mechanism of action of alternating electric fields therapy in GBM, its efficacy in GBM and expected side effects will be discussed. TTFields is a treatment modality that acts on dividing cells by generating therapeutic levels of electric fields. Causing DNA damage and inhibiting DNA repair, activating apoptosis, autophagy and immunogenic death pathways, causing destruction of the cytoskeleton network, causing the formation of pores in the membrane and causing cellular destruction by disrupting cellular ion balance are the effects of alternating electric field therapy on cells. TTFields, which has also been tested in tumors such as lung cancer, pancreatic cancer and malignant mesothelioma, has proven to be a survival-enhancing treatment in primary and recurrent GBM patients. The risk of serious toxicity was found to be very low and the most common side effects were mild and moderate dermatologic toxicities. Having proven its efficacy and safety in GBM patients, TTFields is likely to benefit many more patients if cost issues can be overcome.

Keywords: GBM; toxicity; tumor treating fields.

Copyright © 2026, Turkish Society for Radiation Oncology

INTRODUCTION

Glioblastoma multiforme (GBM) is the most common and most lethal primary brain tumor in adults. It has a highly aggressive course with a 5-year survival rate of 5–7%. [1,2] The disease, which is most commonly seen in the brain, can also be observed in the brain stem, cerebellum and spinal cord more rarely. The median age of onset is 64 years. [3] GBM can occur without a known precursor lesion (primary) or with the transformation of a low-grade tumor over time (secondary). Primary GBM is much more common than second-

ary GBM. Primary GBM, which has a worse prognosis, tends to occur at older ages than secondary GBM. [3–5] There are different genetic alterations that can be seen in GBM patients: Epidermal growth factor receptor (EGFR) overexpression, PTEN mutation and loss of chromosome 10 are especially typical for primary GBM, whereas isocitrate dehydrogenase-1 (IDH1) mutation, TP53 mutation and loss of 19q are seen especially in secondary GBM. [5,6] Especially the identification of IDH1 mutation status stands out as a reliable marker in the molecular differentiation of primary-secondary GBM. The standard treatment in GBM with

Received: October 07, 2025

Accepted: July 14, 2026

Online: September 10, 2026

Accessible online at:

www.onkder.org

Dr. Sıtkı Utku AKAY

Muğla Eğitim ve Araştırma Hastanesi,

Radyasyon Onkolojisi Kliniği,

Muğla-Türkiye

E-mail: suakay91@hotmail.com



good performance is adjuvant chemoradiotherapy and adjuvant temozolomide treatment after maximal surgical resection.[5,7,8] The agent of choice in chemoradiotherapy is temozolomide, as in adjuvant treatment. In addition to this treatment, alternating electric fields or tumor treating fields (TTFields) are also recommended at category 1 level in the NCCN guideline.[9] TTFields is a treatment modality that acts on dividing cells by generating electric fields at therapeutic levels.[10,11] Although alternating electric fields therapy is recommended at category 1 level by the NCCN for the treatment of GBM, many oncology physicians have questions about the efficacy of this treatment and may have difficulties in accessing this costly treatment. In this review, the mechanism of action of alternating electric fields therapy in GBM, its efficacy in GBM and expected side effects will be discussed.

TUMOR TREATING FIELDS THERAPY FOR GLIOBLASTOMA MULTIFORME: EFFECTIVENESS AND SAFETY

The effect of electric field on living cells was demonstrated for the first time in 1922 with a study showing the migration of bacteria in an electric field.[12] Alternating electric field can be used in medicine for nerve-muscle stimulation, acceleration of wound healing and treatment of various muscle and joint diseases.[13,14] Causing DNA damage and inhibiting DNA repair, activating apoptosis, autophagy and immunogenic death pathways, causing destruction of the cytoskeleton network, causing the formation of pores in the membrane and causing cellular destruction by disrupting cellular ion balance are the effects of alternating electric field treatment on cells; mitotic arrest and cell death occur in cells with the help of these mechanisms.[10,11] Giladi et al.[15] showed that TTFields inhibited the repair of radiotherapy-induced DNA damage in glioma cells. In the study conducted by Kirson et al.,[16] it was shown that alternating electric field application had an inhibitory effect on the growth of human and rat tumor cell groups. Analyses have shown that the cytotoxic effect of the electric field on dividing cells is maximum in the range of 150–200 kHz.[17] The treatment was found to have this effect on selectively dividing cells. These findings suggest that electric field therapy may also have a therapeutic role in malignant tumors. In GBM patients, TTFields is administered via a noninvasive and portable device that transmits alternating electric current to the brain via arrays placed on the scalp.

In the pilot study conducted by Kirson et al.[18] 200 kHz TTFields were applied to recurrent GBM patients. In a study of 10 patients, the median time to progression was 26 weeks and median overall survival was 62 weeks. These durations were reported to be approximately 2 times the reported durations for this patient group. The only instrument-related side effect was mild contact dermatitis and no serious side effects were observed. The study concluded that TTFields therapy is an effective and safe treatment modality for human cancers. In a pilot study by Salzberg et al.,[19] 100–200 kHz TTFields was applied to patients with locally advanced and/or metastatic solid tumors. The study included 6 patients who underwent multiple-line treatment. In 1 patient, partial response was observed, and in 3 patients tumor growth stopped during treatment. Disease progression was observed in 1 of the remaining 2 patients, and in the other patient with mesothelioma, regression was observed in the lesion near TTFields, while progression was observed in the lesion in the distant region. No serious treatment-related toxicity was detected. It was emphasized that TTFields is a safe and effective treatment modality that deserves further research. TTFields has also been tested in tumors such as lung cancer, pancreatic cancer and malignant mesothelioma and has been shown to be an effective and safe treatment modality.[20–23] In another study by Kirson et al.,[24] TTFields was administered in combination with temozolomide in newly diagnosed GBM patients. At the end of the study, progression-free survival was 155 weeks and overall survival was +39 months. TTFields treatment did not cause systemic toxicity and did not increase temozolomide-related side effects. It was concluded that TTFields added to chemotherapy increased chemotherapy sensitivity without increasing treatment-related toxicity. In a phase 3 study by Stupp et al.,[25] 200 kHz TTFields were compared with chemotherapy in patients with recurrent GBM. Although there was no significant difference between the groups in terms of overall survival, TTFields was found to be superior in terms of toxicity and quality of life. In a randomized study by Stupp et al.,[26,27] GBM patients were divided into temozolomide or temozolomide + TTFields arms after chemoradiotherapy. TTFields was applied at 200 kHz. As a result of the analysis, progression-free survival and overall survival were significantly higher in the TTFields group in both preliminary and final analysis. In a subgroup analysis of the EF-14 study, increased adherence to TTFields treatment was found to be an independent prognostic factor that increased survival in GBM.[28] In a secondary analysis

of the EF-14 study, it was found that there was no decrease in quality of life in the group that added TTFields to temozolomide compared to the other group, but the side effect of skin itching was observed more in the group that received TTFields.[29] Fallah et al.[30] investigated the efficacy of bevacizumab + TTFields treatment in recurrent GBMs in a phase 2 study. In the study of 23 patients, median progression-free survival was 4.1 months and overall survival was 10.5 months. Grade 3–4 side effects thought to be treatment-related were observed in 2 patients. It was concluded that TTFields treatment is a safe and effective treatment. In a subgroup analysis study on Korean patients included in the EF-14 study, median overall survival and 1 and 2-year survival rates were significantly higher in the group that received TTFields treatment.[31] No serious toxicity was detected and skin irritation was observed in 30% of patients. The results demonstrate once again that TTFields is a safe and effective treatment.

Studies have shown that TTFields is a treatment approach with a low risk of serious toxicity. The most common treatment-related side effect is dermatologic toxicities.[26–33] Allergic dermatitis, irritant dermatitis, ulcers and mechanical lesions are side effects that can occur as dermatologic toxicity. Although topical corticosteroids may be sufficient in the management of dermatologic toxicities, topical-oral antibiotics may also be used in appropriate patients. Scalp cleansing, appropriate shaving and relocation of the instrument are recommended measures to reduce the risk of toxicity.[33]

TTFields is a very expensive treatment and its utilization rate can vary significantly from country to country due to the cost it brings to the healthcare system.[34] While the SEOM-GEINO and ASCO-SNO guidelines state that TTFields can be considered in newly diagnosed GBMs, it is recommended at category 1 level in the NCCN guideline.[9,35,36] Although there is no clear recommended treatment scheme for recurrent GBM, TTFields is one of the treatment options that can be preferred by current guidelines. TTFields, which has proven its efficacy and safety in GBM patients, is likely to benefit many more patients if cost issues are overcome.

CONCLUSION

TTFields is a treatment modality that has proven its efficacy and safety in newly diagnosed and recurrent GBM with its antimitotic and apoptotic effects.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study received no financial support.

Use of AI for Writing Assistance: No AI technologies utilized.

Author Contributions: Concept – S.U.A., O.K.; Design – S.U.A.; Supervision – S.U.A.; Funding – S.U.A., O.K.; Materials – S.U.A.; Data collection and/or processing – S.U.A.; Data analysis and/or interpretation – S.U.A., O.K.; Literature search – S.U.A., O.K.; Writing – S.U.A., O.K.; Critical review – S.U.A., O.K.

Peer-review: Externally peer-reviewed.

REFERENCES

1. Wirsching HG, Galanis E, Weller M. Glioblastoma. *Handb Clin Neurol* 2016;134:381–97.
2. Wu W, Klockow JL, Zhang M, Lafortune F, Chang E, Jin L, et al. Glioblastoma multiforme (GBM): An overview of current therapies and mechanisms of resistance. *Pharmacol Res* 2021;171:105780.
3. Davis ME. Glioblastoma: Overview of disease and treatment. *Clin J Oncol Nurs* 2016;20:2–8.
4. Ohgaki H, Kleihues P. The definition of primary and secondary glioblastoma. *Clin Cancer Res* 2013;19:764–72.
5. Wilson TA, Karajannis MA, Harter DH. Glioblastoma multiforme: State of the art and future therapeutics. *Surg Neurol Int* 2014;5:64.
6. Ohgaki H, Kleihues P. Genetic pathways to primary and secondary glioblastoma. *Am J Pathol* 2007;170:1445–53.
7. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005;352:987–96.
8. Clarke J, Butowski N, Chang S. Recent advances in therapy for glioblastoma. *Arch Neurol* 2010;67:279–83.
9. Nabors LB, Portnow J, Baehring J, Bhatia A, Bloch O, Brem S, et al. NCCN guidelines central nervous system cancers. Version 2.2025-8.28.2025. Available at: <https://virtualtrials.org/pdf2025/cns.pdf>. Accessed Aug 5, 2026.
10. Shams S, Patel CB. Anti-cancer mechanisms of action of therapeutic alternating electric fields (tumor treating fields [TTFields]). *J Mol Cell Biol* 2022;14:mjac047

11. Mun EJ, Babiker HM, Weinberg U, Kirson ED, Von Hoff DD, et al. Tumor-treating fields: A fourth modality in cancer treatment. *Clin Cancer Res* 2018;24:266–75.
12. Northrop JH. The stability of bacterial suspensions: I. A convenient cell for microscopic cataphoresis experiments. *J Gen Physiol* 1922;4:629–33.
13. Sanseverino ER, Vannini A, Castellacci P. Therapeutic effects of pulsed magnetic fields on joint diseases. *Panminerva Med* 1992;34:187–96.
14. Palti Y. Stimulation of internal organs by means of externally applied electrodes. *J Appl Physiol* 1966;21:1619–23.
15. Giladi M, Munster M, Schneiderman RS, Voloshin T, Porat Y, Blat R, et al. Tumor treating fields (TTFields) delay DNA damage repair following radiation treatment of glioma cells. *Radiat Oncol* 2017;12:206.
16. Kirson ED, Gurvich Z, Schneiderman R, Dekel E, Itzhaki A, Wasserman Y, et al. Disruption of cancer cell replication by alternating electric fields. *Cancer Res* 2004;64:3288–95.
17. Swanson KD, Lok E, Wong ET. An overview of alternating electric fields therapy (NovoTTF therapy) for the treatment of malignant glioma. *Curr Neurol Neurosci Rep* 2016;16:8.
18. Kirson ED, Dbalý V, Tovarys F, Vymazal J, Soustiel JF, Itzhaki A, et al. Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. *Proc Natl Acad Sci U S A* 2007;104:10152–7.
19. Salzberg M, Kirson E, Palti Y, Rochlitz C. A pilot study with very low-intensity, intermediate-frequency electric fields in patients with locally advanced and/or metastatic solid tumors. *Onkologie* 2008;31:362–5.
20. Pless M, Droege C, von Moos R, Salzberg M, Betticher D. A phase I/II trial of tumor treating fields (TTFields) therapy in combination with pemetrexed for advanced non-small cell lung cancer. *Lung Cancer* 2013;81:445–50.
21. Giladi M, Weinberg U, Schneiderman RS, Porat Y, Munster M, Voloshin T, et al. Alternating electric fields (tumor-treating fields therapy) can improve chemotherapy treatment efficacy in non-small cell lung cancer both *in vitro* and *in vivo*. *Semin Oncol* 2014;41:S35–41.
22. Babiker HM, Picozzi V, Chandana SR, Melichar B, Kasi A, Gang J, et al. Tumor treating fields with gemcitabine and nab-paclitaxel for locally advanced pancreatic adenocarcinoma: Randomized, open-label, pivotal phase III PANOVA-3 study. *J Clin Oncol* 2025;43:2350–60.
23. Ceresoli GL, Aerts JG, Dziadziuszko R, Ramlau R, Cedres S, van Meerbeeck JP, et al. Tumour treating fields in combination with pemetrexed and cisplatin or carboplatin as first-line treatment for unresectable malignant pleural mesothelioma (STELLAR): A multicentre, single-arm phase 2 trial. *Lancet Oncol* 2019;20:1702–9.
24. Kirson ED, Schneiderman RS, Dbalý V, Tovarys F, Vymazal J, Itzhaki A, et al. Chemotherapeutic treatment efficacy and sensitivity are increased by adjuvant alternating electric fields (TTFields). *BMC Med Phys* 2009;9:1.
25. Stupp R, Wong ET, Kanner AA, Steinberg D, Engelhard H, Heidecke V, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomised phase III trial of a novel treatment modality. *Eur J Cancer* 2012;48:2192–202.
26. Stupp R, Taillibert S, Kanner AA, Kesari S, Steinberg DM, Toms SA, et al. Maintenance therapy with tumor-treating fields plus temozolomide vs temozolomide alone for glioblastoma: A randomized clinical trial. *JAMA* 2015;314:2535–43.
27. Stupp R, Taillibert S, Kanner A, Read W, Steinberg D, Lhermitte B, et al. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: A randomized clinical trial. *JAMA* 2017;318:2306–16.
28. Toms SA, Kim CY, Nicholas G, Ram Z. Increased compliance with tumor treating fields therapy is prognostic for improved survival in the treatment of glioblastoma: A subgroup analysis of the EF-14 phase III trial. *J Neurooncol* 2019;141:467–73.
29. Taphoorn MJB, Dirven L, Kanner AA, Lavy-Shahaf G, Weinberg U, Taillibert S, et al. Influence of treatment with tumor-treating fields on health-related quality of life of patients with newly diagnosed glioblastoma: A secondary analysis of a randomized clinical trial. *JAMA Oncol* 2018;4:495–504.
30. Fallah J, Chaudhary RT, Rogers LR, Wei W, Brewer CJ, Peereboom DM, et al. Clinical outcomes of the combination of bevacizumab and TTFields in patients with recurrent glioblastoma: Results of a phase II clinical trial. *J Clin Oncol* 2020;38:2537–7.
31. Kim CY, Paek SH, Nam DH, Chang JH, Hong YK, Kim JH, et al. Tumor treating fields plus temozolomide for newly diagnosed glioblastoma: A subgroup analysis of Korean patients in the EF-14 phase 3 trial. *J Neurooncol* 2020;146:399–406.
32. Bokstein F, Blumenthal D, Limon D, Harosh CB, Ram Z, Grossman R. Concurrent tumor treating fields (TTFields) and radiation therapy for newly diagnosed glioblastoma: A prospective safety and feasibility study. *Front Oncol* 2020;10:411.
33. Lacouture ME, Davis ME, Elzinga G, Butowski N, Tran D, Villano JL, et al. Characterization and management of dermatologic adverse events with the NovoTTF-100A system, a novel anti-mitotic electric field device for the treatment of recurrent glioblastoma. *Semin Oncol* 2014;41:1–14.

34. Khagi S, Kotecha R, Gatson NTN, Jeyapalan S, Abdullah HI, Avgeropoulos NG, et al. Recent advances in tumor treating fields (TTFields) therapy for glioblastoma. *Oncologist* 2025;30:oyae227.
35. Segura PP, Quintela NV, García MM, Berrón SDB, Sarrío RG, Gómez JG, et al. SEOM-GEINO clinical guidelines for high-grade gliomas of adulthood (2022). *Clin Transl Oncol* 2023;25:2634–46.
36. Mohile NA, Messersmith H, Gatson NT, Hottinger AF, Lassman A, Morton J, et al. Therapy for diffuse astrocytic and oligodendroglial tumors in adults: ASCO-SNO guideline. *J Clin Oncol* 2022;40:403–26.