# Long-term tumour-treating fields for glioblastoma and beyond disease progression: a case report

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## Case report

In May 2018, a 55-year-old Chinese man experienced sudden headache, vomiting and generalised seizures. On hospitalisation, he had a Glasgow Coma Score of 13/15 and global aphasia. Gadolinium contrast-enhanced magnetic resonance imaging revealed a left middle temporal gyrus heterogeneously enhancing intra-axial brain tumour with intratumoural haemorrhage (Fig 1a). A craniotomy for gross total tumour resection was performed under general anaesthesia 1 day after admission (Fig 1b). The patient fully recovered his language ability and was discharged from the hospital 3 days after surgery with no focal neurological deficit. At discharge, he had a Karnofsky Performance Score of 90 and an Eastern Cooperative Oncology Group (ECOG)

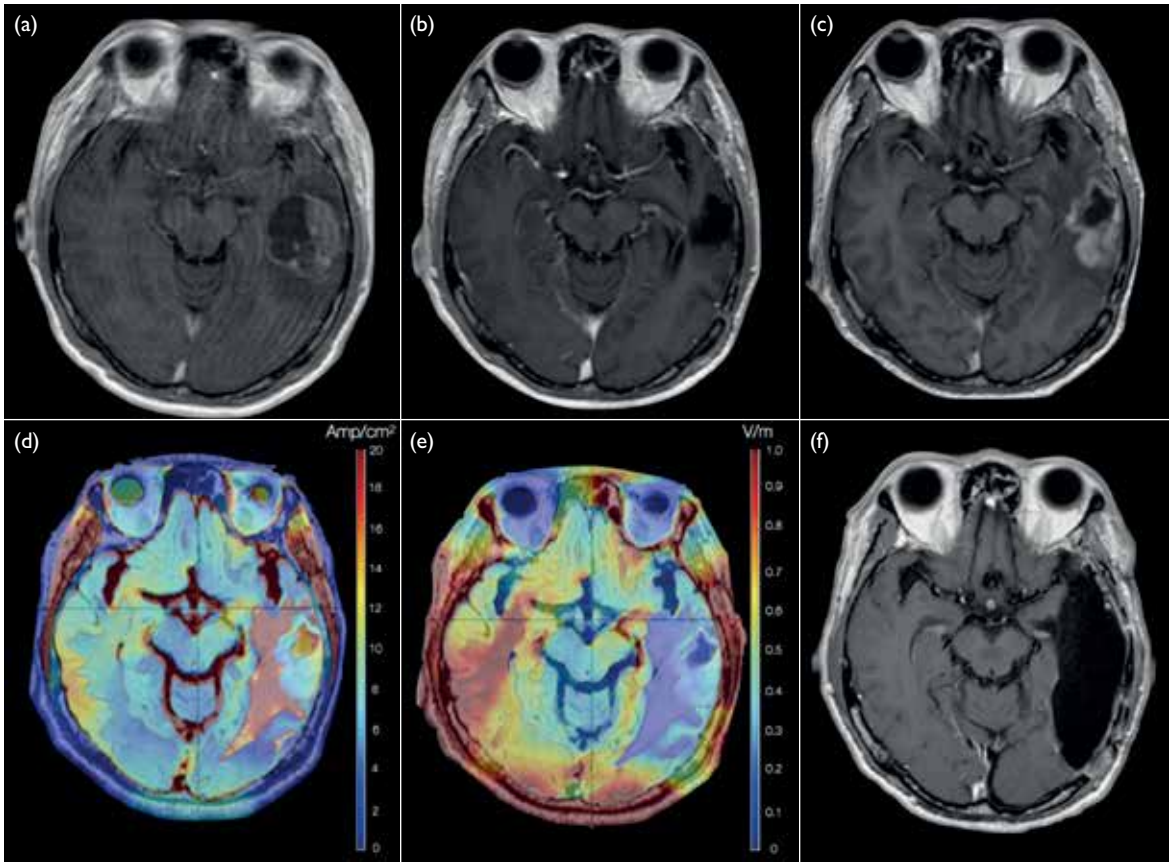


FIG 1. (a) Preoperative axial magnetic resonance imaging: left temporal glioblastoma with intratumoural haemorrhage. (b) After concomitant temozolomide chemoradiotherapy and 5 months of tumour-treating fields (TTF). (c) First disease progression after 12 months of TTF. (d, e) TTF current density (Amp/cm$^2$) and electric field intensity (V/cm) maps revealing increased electromotive force delivery to the peritumoural region after gross total resection of the patient's first tumour recurrence. (f) No evidence of residual tumour 3 years after initial diagnosis and 30 months of TTF

 

performance status of 1. The histopathological diagnosis was glioblastoma (*IDH-1* wildtype, promoter *MGMT* unmethylated). Targeted next-generation gene sequencing revealed the presence of *CDKN2A* homozygous deletion and EGFR amplification, molecular biomarkers associated with a poorer prognosis.[1]

The patient received concomitant temozolomide (TMZ) chemoradiotherapy with a total of 60 Gy of radiation given over 30 fractions. After three adjuvant cycles of TMZ, 6 months after diagnosis, alternating electric field therapy also known as tumour-treating fields (TTF) was started in December 2018. After initiation, the patient was able to return to work as a bartender with a Karnofsky Performance Score of 100 and ECOG status of 0. His mean monthly TTF compliance was 75% and although he experienced grade I scalp skin toxicity (mild dermatitis), this was resolved with topical hydrocortisone cream (Fig 2). The patient received a total of six cycles of TMZ and declined further chemotherapy, relying on TTF alone for tumour control for the next 12 months. His EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer global quality of life) score was 67/100 before TTF, which improved to 84/100 after 6 months. The caregiver stress index, a self-reported measure of primary caregiver burden, was 2 (a threshold of >7 indicates high stress).

There was focal tumour recurrence 18 months after diagnosis and a second craniotomy with supratotal resection was performed in December 2019 (Fig 1c). The patient received six cycles of second-line lomustine chemotherapy and TTF was restarted 6 weeks after the operation. The treatment field plan was adjusted after the second resection to enhance the current density (CD, Amp/cm$^2$) and electric field intensity (EF, V/cm) to the peritumoural regions (Fig 1d and e). The patient's monthly TTF compliance increased to 85% and his ECOG status was 1. After 14 months, in February 2021, there was a second glioblastoma recurrence at the inferior temporal gyrus located beyond the treatment $EF_{50\%}$ and $CD_{50\%}$ isodose regions. An awake craniotomy for language mapping and 5-aminolevulinic acid fluorescent-guided gross total resection was performed. Since the patient's recurrent glioblastoma now had acquired TMZ and lomustine resistance, without effective third-line systemic therapy options, he was promptly restarted on TTF 2 weeks after surgery achieving a mean compliance of 90%. The patient received a further 10 months of TTF monotherapy after his second recurrence, experiencing minimal adverse effects with an ECOG performance status of 1, good quality of life (EORTC 89/100) and no recurrence (Fig 1f). In December 2021, multifocal disease progression with leptomeningeal spread was detected and the patient passed away in February 2022, 45 months (3.8 years) after diagnosis.

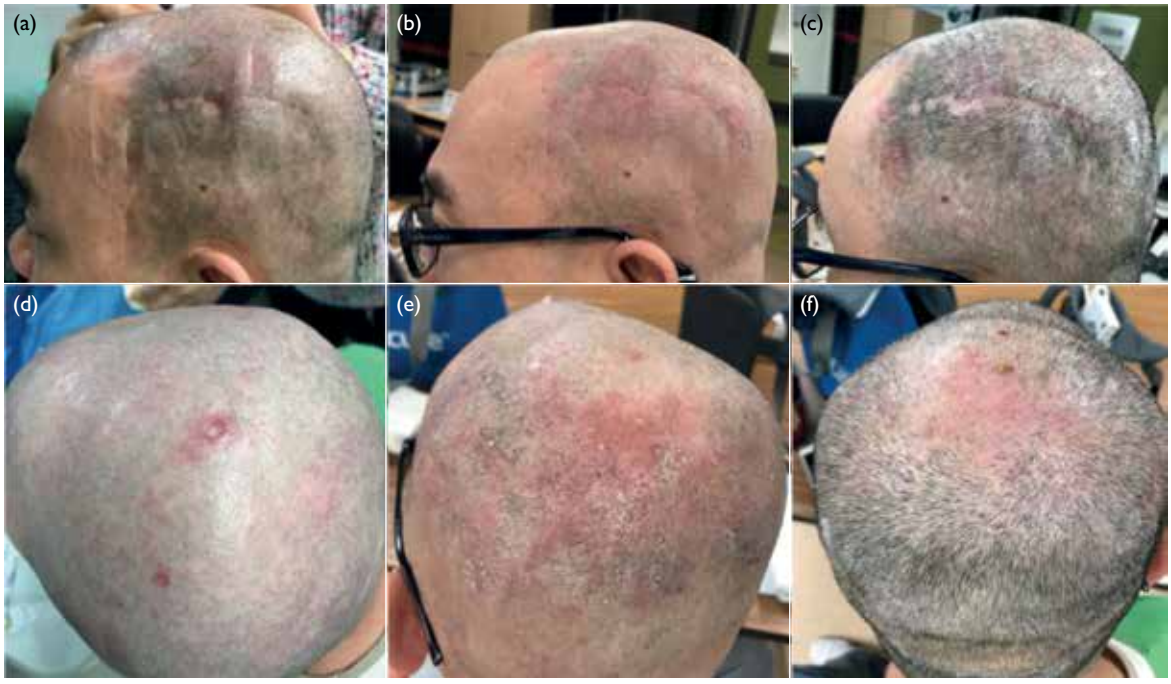


FIG 2. Clinical photographs revealing grade I skin toxicity and its resolution after topical hydrocortisone cream treatment. Lateral views of the craniotomy wound after (a) 1 week, (b) 2 weeks, and (c) 8 weeks of tumour-treating fields; scalp vertex after (d) 1 week, (e) 2 weeks, and (f) 8 weeks of tumour-treating fields

## Discussion

Glioblastoma is the most common primary malignant brain tumour in adults with a prevalence of 3 to 5 per 100 000 population. In Hong Kong, 80 to 100 patients are diagnosed annually. Multimodality standard-of-care treatment has remained unchanged over the last 15 years comprising of maximal safe resection followed by concomitant TMZ chemoradiotherapy.[2] Prognosis nonetheless remains poor and patients have a median overall survival (OS) of only 15 months and for those with an unmethylated *pMGMT* tumour molecular profile, 12 months.[2] Tumour-treating fields is a novel therapy approved by the United States Food and Drug Administration and has been incorporated in several national guidelines as a first-line treatment option for patients with newly diagnosed glioblastoma. The therapy consists of the non-invasive local administration of alternating electric fields of low intensity (1-3 V/cm) and intermediate frequency (200 kHz) to the post-resection region. The mechanism of action involves the exertion of an electromotive force on intracellular proteins critical for mitosis, namely the microtubule substrates tubulin and septin. The antimitotic effect is most pronounced during the tumour cell cycle metaphase when microtubule assembly is disrupted, resulting in aneuploidy, post-mitotic stress, and ultimately apoptosis.[3]

The efficacy of TTF in glioblastoma is well supported by several randomised controlled trials. The landmark EF-14 phase III trial that recruited 695 patients with newly diagnosed glioblastoma revealed a significant increase in median OS among those who received TTF and standard TMZ chemoradiotherapy compared with their control group counterparts that received standard treatment alone (21 vs 17 months; hazard ratio=0.63; 95% confidence interval=0.53-0.76).[3] The 2-year OS rate for patients receiving TTF with standard care was 43% compared with 29% for those that received standard care alone.[3] These findings were independent of conventional predictors of OS such as *pMGMT* methylation status or extent of resection and were validated by subsequent studies. Our patient's glioblastoma carried a relatively poor prognostic molecular profile and to observe his longer-than-expected OS demonstrates how TTF-generated antimitotic electromotive forces remain unaffected by tumour chemoresistance mechanisms. Studies have also documented a dose-response relationship whereby mean monthly treatment compliance, above a threshold of 60%, was associated with improved median OS.[3-5] This phenomenon was also noted in our patient where his first progression-free survival was 12 months with 75% TTF compliance but subsequently increased to 14 months when his compliance was improved to 85%. In general, the median OS of patients with recurrent glioblastoma is 6.5 months and it is encouraging that our experience documented an additional survival benefit from TTF beyond first and second disease progression regardless of the systemic therapy prescribed.[6,7]

The only modifiable predictor for OS is the extent of glioblastoma resection[8] and we believe this played an important role in our patient's response to TTF. There is robust evidence that maximal safe resection, even beyond radiologically defined tumour boundaries (ie, supratotal resection), confers a significant advantage.[9] To this end, awake craniotomy with intra-operative brain mapping and 5-aminolevulinic acid fluorescent guided resection have been proven to be useful surgical adjuncts.[10,11] In contrast, standards of care for systemic treatment at recurrence are much less well-defined.[7,12] Despite limited evidence to support its use, lomustine, a nitrosourea alkylating agent, is the most frequently administered second-line treatment.[12] Randomised controlled clinical trials revealed lomustine treatment response rates to only be in the range of 10%, conferring a median progression-free survival of <2 months.[12,13] Furthermore, lomustine activity is largely restricted to *pMGMT* methylated tumours, which our patient did not have.[12]

Starting in December 2018, Hong Kong was the first Asian region outside of Japan to provide patients with access to TTF. Treatment is generally started as early as 2 weeks after radiotherapy and patients are required to have their hair clipped during the entire period. The electric fields are delivered through disposable adhesive scalp transducer arrays connected to a portable generator with interchangeable batteries, each lasting for 4 hours. Dosimetry in terms of field intensity (V/cm) and current density (Amp/cm$^2$) can significantly influence OS therefore array positioning requires an analysis of magnetic resonance imaging scans to achieve the greatest therapeutic effect (Fig 1).[4]

Scalp arrays are typically changed every 3 days when hair regrowth interrupts their apposition. Patients are required to be constantly connected to the 1.2-kg field generator for at least 15 hours per day. Despite this treatment commitment, reviews of the quality of life of TTF patients report outcomes comparable to those without such therapy.[14] The most common adverse effect, occurring in up to 45% of patients, is scalp dermatitis, which is often mild to moderate in nature and sufficiently managed by temporary array repositioning or topical hydrocortisone.[3] There is no evidence to suggest that patients receiving TTF are at higher risk of developing seizures. The only absolute contra-indications to TTF are the presence of a large skull defect, an active implantable medical device, uncontrolled scalp wound infection, or allergies to adhesive tape or hydrogels.

The TTF therapy is the first breakthrough treatment for glioblastoma in >15 years. As exhibited by our patient, long-term TTF therapy was well-tolerated and conferred a significant benefit in terms of OS.

### Author contributions

Concept or design: PYM Woo, TC Lam.
Acquisition of data: PYM Woo, TC Lam.
Analysis or interpretation of data: PYM Woo, TC Lam.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

### Conflicts of interest

All authors have disclosed no conflicts of interest.

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### Ethics approval

Institutional Review Board of The University of Hong Kong/Hospital Authority Hong Kong West Cluster (Ref No. UW 19-626). Patient consent available upon request.

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