

Fluctuations in areas of contrast enhancement at MRI in a glioblastoma patient treated with tumor-treating electric fields: an hitherto undescribed effect of this treatment modality?

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Use of low-intensity, intermediate frequency electric fields (TTF, or tumor-treating fields) has been investigated in the setting of both recurrent glioblastoma, where it has been shown to be not inferior to other second-line treatments (Stupp, Eur. J. Cancer. 2012), and of de novo glioblastoma, in which preliminary data suggest a strong positive impact both on PFS and on overall survival (Stupp, SNO 2014).

The mechanism(s) of action of TTF include both disruption of mitotic spindle function and induction of engulfment of cytoplasmic organelles during the separation of dividing cells. 1

However, other mechanisms of action may be present, as suggested by studies in models of metastatic brain disease (Kirson, 2009), and effects on tumor cell migration to/within the brain (possibly also involving the blood-brain-barrier) cannot be excluded.

The introduction in glioblastoma therapy of antiangiogenic agents such as bevacizumab in the last years has led to identification of new clinico-radiological patterns (pseudoprogression), whereas pseudoprogression is detected in the phases of concomitant chemoradiation after surgery.

Correct identification of these new clinico-radiological patterns of disease modification is mandatory for appropriate management of glioblastoma.

Recently, Vymazal and Wong (Seminars in Oncology 2014) have described the pattern of response of recurrent glioblastoma in patients treated with TTF; 7 out of 16 responders showed initial tumor growth, suggesting that detection of reduced tumor burden may take some time to develop. However, no fluctuations in areas of contrast enhancement have been described.

Case report.

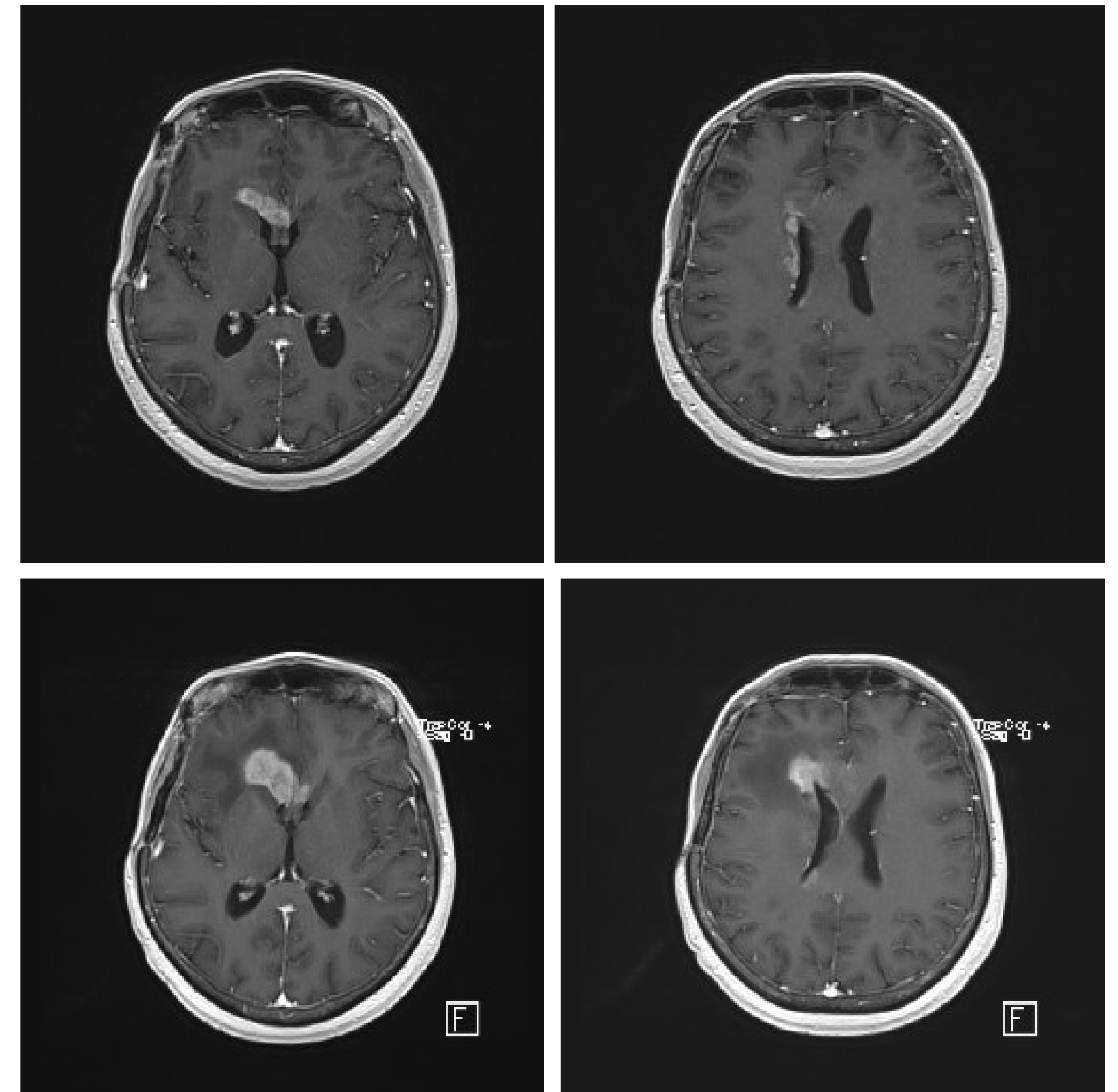
A 54-yr-old lady was operated for right frontal glioblastoma and following surgery she was enrolled in the EF14 trial and randomized to the active TTF treatment arm, receiving concomitant radiotherapy and adjuvant chemotherapy (Stupp protocol) plus TTF after the end of the concomitant phase.

Her clinical conditions remained stable and follow-up MRI showed no disease progression/relapse.

At the planned MRI 15 months after the end of adjuvant chemotherapy, areas of contrast enhancement suggestive for disease progression were detected around the frontal horn of the right lateral ventricle in the the right periventricular region, as well as in the septum.

In consideration of her clinically stable conditions, a decision was taken to check a new MRI within a short time (45 days). In the meantime the patient continued to receive only TTF treatment and levetiracetam.

At the planned follow-up MRI, a clearcut progression was seen in the right frontal horn lesion, while periventricular enhancement was no longer detected



Contrast-enhanced T1-weighted MRI

Upper line: February 26, 2015

Lower line: April 9, 2015

Progression of enhancement of lesion surrounding right frontal horn of the lateral ventricle with septum infiltration and clearance of right periventricular enhancement

The patient showed clinical worsening in the few days preceding follow-up MRI, with episodes of urinary incontinence and memory loss. She was therefore started on second-line chemotherapy with fotemustine and is still alive and ambulatory after 6 months.

The observed fluctuations in the MRI pattern have not been described before, and were observed long after the end of post-surgical treatments, except for TTF; they may either reflect the «natural» history of the disease or an effect of TTF at the level of the blood-brain-barrier

[NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality.](#)

Stupp R, Wong ET, Kanner AA, Steinberg D, Engelhard H, Heidecke V, Kirson ED, Taillibert S, Liebermann F, Dbalý V, Ram Z, Villano JL, Rainov N, Weinberg U, Schiff D, Kunschner L, Raizer J, Honnorat J, Sloan A, Malkin M, Landolfi JC, Payer F, Mehdorn M, Weil RJ, Pannullo SC, Westphal M, Smrcka M, Chin L, Kostron H, Hofer S, Bruce J, Cosgrove R, Paleologous N, Palti Y, Gutin PH. Eur J Cancer. 2012 Sep;48(14):2192-202.

[Alternating electric fields \(TTFs\) inhibit metastatic spread of solid tumors to the lungs.](#) Kirson ED, Giladi M, Gurvich Z, Itzhaki A, Mordechovich D, Schneiderman RS, Wasserman Y, Ryffel B, Goldsher D, Palti Y. Clin Exp Metastasis. 2009;26(7):633-40. doi: 10.1007/s10585-009-9262-y. Epub 2009 Apr 23.

Response pattern of recurrent glioblastomas treated with tumor-treating fields. Vymazal J., Wong E., Seminars in oncology 2014, Vol 41, S14-S24