

In vivo study using Tumor Treatment Fields (TTFs) and prolonged mild hyperthermia as adjuvant methods for cancer treatment.

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Delivery of the so called Tumor Treatment Fields (TTFs) was proposed a few years ago as a cancer therapy and has been object of study in a recent phase III trial in which their efficacy against glioblastomas was assessed with modest results [1]. TTFs are alternating electric fields at a frequency in the order of 100 kHz and a magnitude below 300 V/m which are applied continuously for weeks. According to their proposers, TTFs inhibit tumor growth by interfering with the cell division process through electrical forces without causing significant heating in tissues. However, we estimate that TTFs are capable of producing temperature increases of about some tens of kelvin which cannot be neglected, particularly because TTFs are applied for long periods of time. Therefore, we hypothesized that the promising results reported in initial *in vitro* and *in vivo* studies on the use of TTFs could be mediated by heat rather than by electrical forces. Heat induction (i.e. hyperthermia) has been extensively used as an adjuvant in cancer treatment. Typically, cancer hyperthermia involves generating moderate temperature increases during about one hour after radiotherapy or chemotherapy sessions. Nevertheless, to the best of our knowledge, there are no *in vivo* studies on the use of mild hyperthermia for long periods of time, despite there are *in vitro* studies showing that cell survival to hyperthermia depends both on the temperature and the exposition time.

In order to test our hypothesis and also to independently validate the efficacy of TTFs, we have carried out a study in which nude mice subcutaneously implanted with human exocrine pancreatic adenocarcinomas were physically treated for 7 days; either with heat from a resistor or with TTFs delivered by electrodes. The animals were paired: one was treated and the other was sham treated. Four treatment groups were created: hyperthermia (H) ($n=5+5$), hyperthermia + gemcitabine chemotherapy (H&Ch) ($n=6+6$), TTFs (TTF) ($n=5+5$) and TTFs + gemcitabine therapy (TTF&Ch) ($n=7+7$).



Left: Applicators for both physical treatment modalities. Center: mouse wearing the electric field treatment system. Right: Box-plot results of tumor growth difference for each treatment group.

Our hypothesis has not been validated: no statistically significant effects were observed in the H and H&Ch groups. On the other hand, although the TTF group did also not produce any significant effect, the animals treated with the TTFs + chemotherapy combination show a tumor growth rate about 200% smaller ($p=0.018$) than the animals treated only with chemotherapy.

[1] R. Stupp 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.*, vol 48, no. 14, pp. 2192-2202, 2012.