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LETTER TO THE EDITOR

"Nanomania" *ante portas* of neurooncology?

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To the Editor

There is currently no standard of care for recurrent glioblastoma. Accordingly, there is an urgent medical need for new therapeutic approaches in this setting. Novel treatment approaches are often received with great hopes by patients and relatives. Nevertheless, it is mandatory that all novel treatment approaches, not only pharmacological treatments, are subjected to standardized evaluations of safety and efficacy.

In this regard, German neuro-oncologists have been exposed to pressure from patients and relatives to introduce the new therapy referred to as *intratumoral thermotherapy*, developed by MagForce Nanotechnologies, for many years. Finally and fortunately, data of a "phase II trial" were recently published in the *Journal of Neuro-Oncology* [1]. In contrast to the title of this article, we would like to point out that neither safety nor efficacy were demonstrated:

(i) Safety was an issue. 15 patients experienced epileptic seizures in the context of the treatment. Even the authors raise the possibility that patients might benefit from prophylactic anticonvulsants if they opt for this treatment modality. From the quality of life perspective, it is important to note that all metallic materials including dental fillings, crowns and implants within 40 cm of the treatment area had to be removed, for safety reasons.

(ii) Efficacy could not be demonstrated simply as a consequence of the study design. The experimental treatment was combined with fractionated stereotactic radiotherapy at 30 Gy in 2 Gy fractions. The combination of an experimental treatment modality with an established treatment modality like stereotactic radiotherapy in an uncontrolled phase II trial is inappropriate to demonstrate efficacy.

(iii) 24 of 59 patients had some treatment (resection 11, radiotherapy 2, chemotherapy 17) for the same recurrence subsequently treated with intratumoral thermotherapy. No effort was made to dissect the role of the various treatment measures administered at recurrence.

(iv) The authors indicate that "data on any subsequent treatments for tumor progression following the thermo/radiotherapy were not systematically collected". Accordingly, the impact of the experimental treatment on the overall survival estimate is impossible to evaluate. Progression-free survival was not assessed and cannot easily be addressed since this treatment precludes further MRI monitoring for life because of artefact. Yet, overall survival at 2 years from recurrence was the primary end point and additional treatment measures at further recurrence are likely to have influenced the treatment results.

(v) The authors state that analysis was by intention to treat, but it remains unclear what happened to the seven patients that were included, but did not fulfil inclusion criteria. Curiously, analysis of efficacy is based on 59 patients whereas analysis of safety is on 66 patients.

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Some minor comments need to be made, too:

(vi) The authors claim that randomization for recurrent glioblastoma is "extremely difficult" and that a randomized assessment of intratumoral thermotherapy was not possible. This statement is proven wrong by the series of randomized trials in that setting that have been performed in the recent years, both using local treatments such as immunotoxins or chemotherapy, e.g. for cilengitide [2], erlotinib [3], enzastaurin [4] or cediranib [5].

(vii) The authors cite Stummer et al. [6] as a reference for the value of surgery for recurrent glioblastoma which is not the content of this work.

(viii) The hypothesis that PET and SPECT are as good as MRI to monitor disease progression has never been addressed in a clinical study.

Altogether, this trial has a study design that a priori did not allow to draw conclusions regarding efficacy. Yet, substantial efforts are made in claiming efficacy in the Discussion section, based on historical comparisons which are inappropriate. This unjustified claim of efficacy is worrisome because two of the authors are employees of MagForce Nanotechnologies. This is mentioned as a disclosure, but the conflict of interest section says "none".

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