Author's response to reviews

Title: The radiosensitising effect of gemcitabine and its main metabolite dFdU under low oxygen conditions is in vitro not dependent on functional HIF-1 protein

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Author's response to reviews: see over
Dear Madam, Sir,

As a previous author, I was glad to receive an invitation to submit to *BMC Cancer* recently. So please find enclosed a manuscript entitled "The radiosensitising effect of gemcitabine and its main metabolite dFdU under low oxygen conditions is not dependent on functional HIF-1 protein" submitted for your kind consideration for publication as a research article in *BMC Cancer*.

As radiotherapy is currently utilized in about 50% of patients with solid tumours at some stage of their treatment, a continuing endeavour in experimental and translational oncology research has been to overcome radioresistance and to sensitize tumour cells for the cytotoxic effects of radiation. In addition, tumour hypoxia represents a significant challenge to the curability of human tumours, inducing treatment resistance to both chemotherapy and radiation.

The study presented in the manuscript shows that gemcitabine, an antimetabolite commonly used in clinical practice, retains its radiosensitising potential under low oxygen conditions in breast cancer cell lines. Importantly, for the first time, radiosensitisation by dFdU, the main metabolite of gemcitabine, was investigated and demonstrated under low oxygen conditions. As dFdU has a prolonged half-life, the sustained presence of dFdU in the blood might induce radiosensitisation despite the short half-life of the parent drug gemcitabine. This might be highly relevant, especially considering delivery of the drug to hypoxic tumour regions. No major role for functional hypoxia-inducible factor 1 (HIF-1) in radiosensitisation by gemcitabine or dFdU could be demonstrated, as HIF-1 proficient and HIF-1 deficient cells were equally radiosensitised.

We are convinced that these observations form a solid basis for further *in vivo* and clinical studies on this topic. The paper presents and discusses original data and demonstrates a potentially promising application to the future practice of medicine.

As requested, we now included line numbers in the document. Neither this manuscript nor any similar paper has been submitted to any other scientific journal. All of the authors are aware of and agree to the content of the manuscript.

Yours sincerely,

dr. An Wouters