

are currently performed in order to establish an effective radiosensitizing treatment modality.

EP-2324 Non-invasive PET imaging of radiosensitive tumour regions using γ H2AX-targeted immunoconjugate

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Purpose or Objective

It has previously been demonstrated that radiation-induced residual γ H2AX foci represent a sensitive marker of intrinsic radiosensitivity of tumour cells. With the aim to non-invasively visualize radioresistant tumour regions for dose escalation using dose painting approaches, we evaluated the uptake of a ⁸⁹Zr-labelled anti- γ H2AX antibody, modified with the cell penetrating peptide (TAT), which includes a nuclear localization sequence, in a rat rhabdomyosarcoma tumour model.

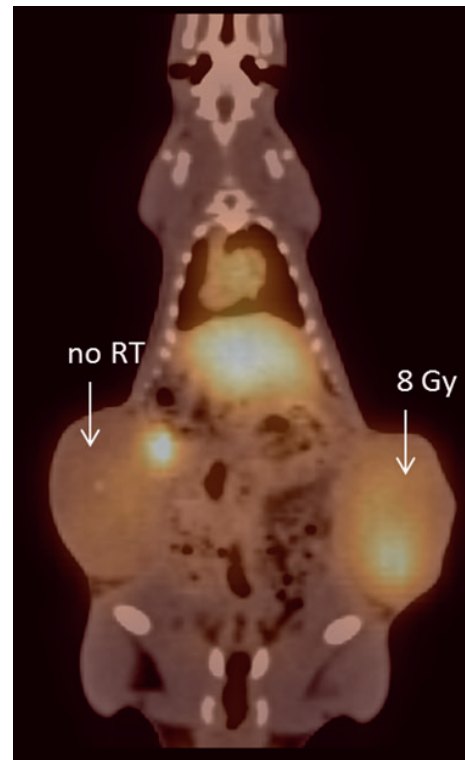
Material and Methods

Rhabdomyosarcoma tumour pieces were transplanted subcutaneously on contralateral flanks in immuno-competent rats (n=4). At average tumour volume of 7.4 cm³, rats were scanned on a clinical PET/CT 3 hours after administration of the hypoxia tracer ¹⁸F-HX4 (~19 MBq), followed by irradiation (8 Gy single dose) of one tumour per rat 18 hours later. One hour after irradiation, the ⁸⁹Zr-anti- γ H2AX-TAT immunoconjugate (~18 μ g, 11 MBq) was injected and uptake was evaluated at 3, 6, 12, 21 and 71 hours after irradiation. After the last imaging time point, tumour tissue and organs were dissected for subsequent γ -counting, autoradiography and histological evaluation.

Results

TBR and SUVmean for ⁸⁹Zr-anti- γ H2AX-TAT as well as difference in uptake between irradiated and non-irradiated tumours increased with increasing time after irradiation (71 hours: SUVmean of 0.44 vs. 0.29, respectively, p=0.03, Figure 1). Similarly, γ -counting revealed higher uptake of ⁸⁹Zr-anti- γ H2AX-TAT in irradiated compared to non-irradiated tumours (0.59 vs. 0.36 %ID/g, respectively, p=0.004). There was a tendency for higher uptake of ⁸⁹Zr-anti- γ H2AX-TAT in hypoxic subvolumes, defined as 30% of the tumour volume with the highest ¹⁸F-HX4 uptake, in both irradiated and non-irradiated tumours. Analysis at microregional level revealed predominant accumulation of ⁸⁹Zr-anti- γ H2AX-TAT in (peri)necrotic regions. Across normal organs, the highest uptake of the tracer was found in the spleen.

Figure 1. An example of uptake of ⁸⁹Zr-anti- γ H2AX-TAT in irradiated and non-irradiated tumours 71 hours post irradiation.



Conclusion

Predominant accumulation of the ⁸⁹Zr-anti- γ H2AX-TAT immunoconjugate in (peri)necrotic regions, despite the higher uptake in irradiated compared to non-irradiated tumours, does not support the use of this probe to image radioresistant tumour regions for dose painting purposes in this rat rhabdomyosarcoma tumour model.

EP-2325 A novel small molecule inhibitor of MRCK prevents radiation driven invasion in glioblastoma

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Purpose or Objective

Glioblastoma (GBM) is an aggressive and incurable primary brain tumour that causes severe neurological, cognitive and psychological symptoms. Symptoms are caused and/or exacerbated by the infiltrative properties of GBM cells, which enable them to pervade the healthy brain, disrupting normal function. Recent research has indicated that, while radiotherapy extends life expectancy of patients, it can provoke a more infiltrative phenotype in those GBM cells that survive treatment. In this study we investigate the role of the actin-myosin regulatory kinase, MRCK, in radiation driven infiltration by GBM cells and probe its potential as an anti-invasive target using a novel MRCK specific inhibitor.

Material and Methods

In vitro motility assays with single cell tracking were used to measure the migration speed of GBM cells on a petri dish. The results were confirmed using an *ex vivo* assay that uses confocal time-lapse microscopy and single cell tracking to measure the speed of GBM cells migrating through fresh murine brain slices.