Göteborg, 2016

Multiparametric MRI for evaluation of tumour treatment response

Studies of ^{177}Lu-octreotate therapy of neuroendocrine tumour

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin,
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av

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Avhandlingen baseras på följande delarbeten:

I. Mikael Montelius, Maria Ljungberg, Michael Horn, Eva Forssell-Aronsson, **Tumour size measurement in a mouse model using high resolution MRI**, *BMC Medical Imaging,* 2012, **12**:12

II. Oscar Gustafsson, Mikael Montelius, Göran Starck, Maria Ljungberg, **Impact of Prior Distributions and Central Tendency Measures in Bayesian Intravoxel Incoherent Motion Model Fitting**, Manuscript

III. Mikael Montelius, Oscar Gustafsson, Johan Spetz, Ola Nilsson, Eva Forssell-Aronsson, Maria Ljungberg, **Multiparametric MR evaluation of small intestine neuroendocrine tumour tissue characteristics correlated to histological analyses**, Manuscript

IV. Mikael Montelius, Johan Spetz, Oscar Gustafsson, Evelin Berger, Ola Nilsson, Maria Ljungberg, Eva Forssell-Aronsson, **Identification of potential MR derived biomarkers for tumour tissue response to ^{177}Lu-octreotate therapy in an animal model of small intestine neuroendocrine tumour**, Manuscript

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER

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Abstract

Clinical assessment of tumour response to treatment largely relies on estimates of tumour size by, *e.g.*, measuring the largest tumour diameters on magnetic resonance (MR) or computed tomography (CT) images, weeks or months after treatment. However, most tumours are heterogeneous, and treatment may result in different effects in different parts of the tumour. Therefore, non-invasive methods sensitive to biological effects that precede changes in tumour size would improve our understanding of tumour biology and therapeutic effects, facilitate personalized treatments and speed up development of anti-cancer therapeutics. MR methods have the potential to provide non-invasive imaging biomarkers of the relevant tumour biology, but the understanding of the information provided by MR methods is still limited.

The aim of this project to was to improve the understanding and evaluate the feasibility of multiparametric MR methods for therapy response assessment of tumours after radionuclide therapy.

Mice xenografted with human neuroendocrine tumours received 15 MBq 177Lu-octreotate i.v. on day 0, and MR imaging experiments were performed on days -1, 1, 3, 8 and 13, using dynamic contrast enhanced-, quantitative T1 and T2*- and diffusion weighted MR on a 7T small animal MR system. Optimization studies were performed to improve tissue model parameter estimates, and to ensure accurate MR based tumour volume estimation for response verification. MR parameter maps were spatially registered to corresponding histologically stained tumour section for correlation analysis, and tumour tissue samples were analysed using quantitative proteomics.

Several statistically significant correlations were found between MR parameters and histological tumour characteristics, as well as with proteins associated with radiobiological effects on tumours, and collectively evaluated they provided information on apoptotic and proliferative activity, microvascular density and fibrosis in tumours, which are all important prognostic tumour characteristics. Spatial and temporal MR parameter variations before and after therapy seem to be predictive of tumour shrinkage or stabilization. Most effects on MR parameters were seen already one day after treatment initiation.

This work demonstrates the feasibility of multiparametric MR for therapy response assessment in an animal tumour model, and highlights the importance of spatial and temporal evaluation of the MR parameters. Future efforts should include improvement of methods for spatial registration of in vivo MR images and ex vivo histological sections. For clinical applications, MR acquisition times need to be reduced.

Keywords: Cancer, Functional imaging, IVIM, MRI, DWI, DCE, histology, ^{177}Lu-octreotate, small intestine neuroendocrine tumour, NET, diffusion, perfusion, semi-quantitative, proteomics, ionizing radiation, biology, imaging biomarker

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