Targeted radiotherapy of metastatic neuroendocrine tumours - Clinical and experimental studies

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Hjärtats aula, Blå stråket 5, Sahlgrenska Universitetssjukhuset, Göteborg, fredagen den 23 november kl. 13.00

av

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Avhandlingen baseras på följande delarbeten

I.   **Treatment with ^{177}Lu-DOTATATE for metastasized NET – long-term effects and a tumour dosimetry model.** Elf AK, Marin I, Rossi Norrlund R, Svensson J, Wängberg B, Nilsson O, Bernhardt P, Johanson V. *In manuscript*

II.   **Can SSTR2 expression in previously resected SI-NETs predict overall survival after PRRT treatment of remaining lesions?** Elf AK, Johanson V, Marin I, Bergström A, Nilsson O, Svensson J, Wängberg B, Bernhardt P, Elias E. *In manuscript*

III. **NAMPT Inhibitor GMX1778 Enhances the Efficacy of ^{177}Lu-DOTATATE Treatment of Neuroendocrine Tumours.** Elf AK, Bernhardt P, Hofving T, Arvidsson Y, Forsell-Aronsson E, Wängberg B, Nilsson O, Johanson V.
Journal of Nuclear Medicine 2017; 58(2):288-292

IV.   **Radioembolization Versus Bland Embolization for Hepatic Metastases from Small Intestinal Neuroendocrine Tumors: Short-term Results of a Randomized Clinical Trial.** Elf, AK, Andersson M, Henriksson O, Jalnefjord O, Ljungberg M, Svensson J, Wängberg B, Johanson V.
World Journal of Surgery 2018; 42:506-513

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Targeted radiotherapy of metastatic neuroendocrine tumours

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ABSTRACT

Neuroendocrine tumours (NET) often present at a metastatic stage, which diminishes the possibility for curative surgery. Peptide receptor radiotherapy (PRRT) with ^{177}Lu-DOTATATE targets somatostatin receptors, which are overexpressed on NET cells. PRRT results in symptom relief and often tumour control of NETs, but rarely cure. Tumour response is variable and renal and haematological toxicity are dose-limiting side effects.

In metastatic small intestinal NET (SI-NET) hepatic metastases are often a clinical problem. Several treatment options exist and radioembolization (RE) of the liver is a recently introduced therapy. Diffusion weighted MRI (DWI) is a new imaging technique reflecting the microenvironment of tumours and is maybe useful for treatment response evaluation.

Aims of the thesis project were to identify predictive factors for response and long-term outcome after PRRT, and investigate a possibility for radiosensitization. Further, RE was compared to hepatic artery embolization (HAE) for SI-NET hepatic metastases, and the utility of DWI as a predictor for morphologic treatment response was investigated.

A retrospective study of 51 NET patients treated with ^{177}Lu-DOTATATE revealed an objective response rate of 13%, however most patients responded with halted tumour growth. High tumour proliferation rate, but not diagnosis, was associated with shorter survival. Overall long-term toxicity was low. The absorbed tumour dose varied considerably within and between patients, but the median absorbed tumour dose was correlated with tumour shrinkage.

In a retrospective study on stage IV SI-NET, patients with low somatostatin receptor 2 (SSTR2) expression did not have an inferior outcome after PRRT. In contrast, a tendency was found towards both higher activity uptake after PRRT and longer survival.

In an experimental animal study, the NAMPT inhibitor GMX1778 enhanced the efficacy of ^{177}Lu-DOTATATE and almost eradicated all tumours.

In a clinical prospective study on SI-NET hepatic metastases, HAE resulted in earlier tumour shrinkage than RE, and the response at 3 months was correlated with DWI after 1 month. A low baseline apparent diffusion was correlated with a larger tumour shrinkage at 6 months.

In conclusion, tumour grade can predict long-term outcome after PRRT in metastatic NET and tumour dosimetry can be useful for response prediction. Low SSTR2 expression should not exclude patients from PRRT. GMX1778 might be used as a radiosensitizer in PRRT for SI-NET. DWI can be useful for prediction and early evaluation of treatment response after RE and HAE for liver metastasized SI-NET.

Keywords: neuroendocrine tumour, peptide receptor radionuclide therapy, somatostatin receptor 2 expression, radiosensitization, radioembolization, diffusion weighted imaging