

Strategies for optimisation of ^{177}Lu -octreotate therapy – exploring local administration and combination therapy regimens

Akademisk avhandling

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Avhandlingen baseras på följande delarbeten

- I. Sandblom V, Ståhl I, Olofsson Bagge R, Forssell-Aronsson E. *Evaluation of two intraoperative gamma detectors for assessment of ^{177}Lu activity concentration in vivo*. EJNMMI Physics 2017; 4(3): 1-15.
- II. Sandblom V, Ståhl I, Hansson C, Olofsson Bagge R, Forssell-Aronsson E. *Local treatment of liver metastases by administration of ^{177}Lu -octreotate via isolated hepatic perfusion – a preclinical simulation of a novel treatment strategy*. Submitted.
- III. Sandblom V, Spetz J, Shubbar E, Montelius M, Ståhl I, Swanpalmer J, Nilsson O, Forssell-Aronsson E. *Gemcitabine potentiates the anti-tumour effect of radiation on medullary thyroid cancer*. Submitted.
- IV. Sandblom V, Spetz J, Shubbar E, Montelius M, Ståhl I, Swanpalmer J, Nilsson O, Forssell-Aronsson E. *Increased therapeutic effect on medullary thyroid cancer using a combination of radiation and tyrosine kinase inhibitors*. Manuscript.
- V. Hofving T, Sandblom V, Arvidsson Y, Shubbar E, Altiparmak G, Swanpalmer J, Almobarak B, Elf AK, Johanson V, Elias E, Kristiansson E, Forssell-Aronsson E, Nilsson O. *^{177}Lu -octreotate therapy for neuroendocrine tumours is enhanced by Hsp90 inhibition*. Endocrine-Related Cancer 2019; 26(4): 437-449.

**SAHLGRENKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER**



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Abstract

Neuroendocrine tumours (NETs) are a group of heterogeneous tumour types that originate in hormone-producing organs. Patients with NETs are often diagnosed after the primary tumour has metastasised. One treatment option for these patients that has shown very promising results is systemic treatment using the radiolabelled somatostatin analogue ^{177}Lu -octreotate. However, the outcome of this treatment is currently restricted by healthy organs at risk.

The aim of this work was to optimise ^{177}Lu -octreotate therapy of NETs by investigating strategies based on local administration and on combination therapy regimens.

The feasibility of local treatment of liver metastases was evaluated by administering ^{177}Lu -octreotate via isolated hepatic perfusion (IHP) in a pig animal model. During IHP, the liver was completely isolated from the systemic circulation. An intraoperative gamma detector was evaluated for the purpose of determining ^{177}Lu activity concentration in vivo during treatment. This detector was also evaluated by assessment of its technical performance parameters using phantoms. In summary, the results showed that it could be feasible to treat patients with liver metastases from NETs with ^{177}Lu -octreotate via IHP. A relatively inhomogeneous uptake was obtained and to accurately quantify ^{177}Lu activity concentration using an intraoperative gamma detector, measurements may need to be performed at several positions over the liver.

In the combination therapy experiments, nude mice transplanted with NETs were treated with radiation therapy alone (as ^{177}Lu -octreotate or external beam radiotherapy) and in combination with one of the drugs gemcitabine, vandetanib, cabozantinib, or ganetespiib. After treatment, tumour volume was followed and compared with that in control mice. Overall, combination treatment resulted in the largest decrease in tumour volume and the longest time to progression. The results indicated that additive, and sometimes synergistic, effects could be obtained when combining ^{177}Lu -octreotate with another drug for treatment of patients with NETs.

Keywords: Peptide receptor radionuclide therapy, PRRT, ^{177}Lu -octreotate, neuroendocrine tumours, optimisation, local administration, combination therapy