

# Aspects on Diagnosis and Treatment of Gastrointestinal Neuroendocrine Tumours

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Göteborgs Universitet kommer att offentligens försvaras i hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, Göteborg, torsdag 25 mars, kl 9.00

av

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Avhandlingen baseras på följande delarbeten:

- I. Chromogranin A as a determinant of midgut carcinoid tumour volume. Lars Kölby, Peter Bernhardt, Christina Swärd, Viktor Johanson, Håkan Ahlman, Eva Forssell-Aronsson, Mats Stridsberg, Bo Wängberg, Ola Nilsson.  
Regulatory Peptides, **120**, 269-273, 2004.
- II. Comparison of [<sup>177</sup>Lu-DOTA<sup>0</sup>-Tyr<sup>3</sup>]-octreotate and [<sup>177</sup>Lu-DOTA<sup>0</sup>-Tyr<sup>3</sup>]-octreotide for receptor-mediated radiation therapy of the xenografted human midgut carcinoid tumor GOT1. Christina Swärd, Peter Bernhardt, Viktor Johanson, Anneli Schmitt, Håkan Ahlman, Mats Stridsberg, Eva Forssell-Aronsson, Ola Nilsson, Lars Kölby.  
Cancer Biotherapy & Radiopharmaceuticals, **23:1**, 114-120, 2008.
- III. Prolonged survival after hepatic artery embolization in patients with midgut carcinoid syndrome. Christina Swärd, Viktor Johanson, Els Nieveen van Dijkum, Svante Jansson, Ola Nilsson, Bo Wängberg, Håkan Ahlman, Lars Kölby.  
British Journal of Surgery, **96**, 517-521, 2009.
- IV. [<sup>177</sup>Lu-DOTA<sup>0</sup>-Tyr<sup>3</sup>]-octreotate treatment in patients with disseminated gastroenteropancreatic neuroendocrine tumours: The value of measuring absorbed dose to the kidney. Christina Swärd, Peter Bernhardt, Håkan Ahlman, Bo Wängberg, Eva Forssell-Aronsson, Maria Larsson, Johanna Svensson, Rauni Rossi-Norrlund, Lars Kölby.  
World Journal of Surgery, published online, 12 January 2010.
- V. Somatostatin receptor-based radiotherapy as treatment for neuroendocrine tumour recurrences after liver transplantation. Christina Swärd, Lars Kölby, Peter Bernhardt, Els Nieveen van Dijkum, Dik Kwekkeboom, Rauni Rossi-Norrlund, Christian Cahlin, Eva Forssell-Aronsson, Michael Olausson, Håkan Ahlman.  
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## ABSTRACT

### Aspects on Diagnosis and Treatment of Gastrointestinal Neuroendocrine Tumours

**Background.** Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) originate from endocrine cells of the intestinal mucosa and pancreas. The tumour cells contain chromogranin A (CgA) and usually have a high expression of somatostatin receptors (SSTR), which can be used for diagnosis and treatment. The treatment alternatives in patients with disseminated GEP-NETs include debulking surgery, hepatic arterial embolization (HAE), in selected cases orthotopic liver transplantation (OLT), or somatostatin receptor (SSTR)-mediated radiation therapy besides medical treatment with somatostatin analogues, interferon, or combination of cytotoxic drugs.

**Material & Methods.** A xenograft model with a transplantable midgut carcinoid tumour (GOT 1) was used to study the correlation between tumour weight and the tumour marker chromogranin A (CgA) in plasma as well as the therapeutic effects of the somatostatin analogue octreotide. The uptake and biodistribution of the radiopharmaceuticals  $^{177}\text{Lu}$ -octreotide and  $^{177}\text{Lu}$ -octreotate in GOT 1-bearing nude mice were studied. A consecutive series of 107 patients treated with HAE was analyzed regarding biochemical response and survival. The effect of SSTR-mediated radiation therapy was analysed in a consecutive series of 26 patients with disseminated GEP-NETs as well as in 6 patients with non-resectable recurrence of tumour after OLT. The absorbed dose to the kidney as a tool for optimization of radiotherapy was evaluated.

**Results.** In GOT 1-bearing nude mice there was a strong correlation between tumour weight and P-CgA ( $P < 0.00001$ ). The P-CgA/tumour weight ratio was significantly lowered by octreotide ( $P < 0.037$ ). The uptake of  $^{177}\text{Lu}$ -octreotate was twice that of  $^{177}\text{Lu}$ -octreotide ( $P = 0.00061$ ) and the reduction of tumour volume was significantly higher in animals given  $^{177}\text{Lu}$ -octreotate ( $P = 0.003$ ). The tumour volume correlated significantly with P-CgA, which served as a marker of treatment effect. A good biochemical response with decreased tumour markers correlated with prolonged survival in patients after HAE ( $P = 0.003$ ). There was also a significant correlation between the responses to primary and repeat HAE. SSTR-mediated radiation therapy resulted in 38% partial tumour reduction according to RECIST-criteria. By using the absorbed dose to the kidney as a limiting factor for therapy we found that 10 patients received fewer than 4 treatments but 4 patients were identified as candidates for additional treatment. There was a significant reduction of glomerular filtration rate (GFR) after radiotherapy ( $P = 0.0013$ ). Also in transplanted patients SSTR-mediated radiation therapy could be used to treat tumour recurrence.

**Conclusions.** 1. P-CgA was well suited for monitoring of the tumour burden and tumour response in GOT 1-bearing nude mice. 2.  $^{177}\text{Lu}$ -octreotate was a more suitable radiopharmaceutical than  $^{177}\text{Lu}$ -octreotide and the *in vivo* data allowed accurate determination of absorbed dose. 3. HAE provided prolonged survival in biochemically responsive patients. Repeat HAE can be considered in patients with favourable response to the first procedure. 4. Calculation of the accumulated dose to the kidneys during SSTR-mediated radiotherapy was valuable to optimize the treatment. 5. SSTR-mediated radiotherapy was a treatment option also for patients with non-resectable recurrence of SSTR-expressing tumours, previously treated with OLT.

**Key words:** Carcinoid, endocrine pancreatic tumour, neuroendocrine, octreotide, somatostatin receptor, peptide receptor radionuclide therapy, absorbed dose, chromogranin A, liver transplantation.

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