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# Improvement of $^{177}$Lu-octreotate treatment of small-intestine neuroendocrine tumors by hyperfractionation

**Akademisk avhandling**

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Wallenbergsalen, Medicinaregatan 20A, den 15 december, klockan 09:00

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## Avhandlingen baseras på följande delarbeten

I. Elvborn, M., Shubbar, E., & Forssell-Aronsson, E. (2022). Hyperfractionated Treatment with $^{177}$Lu-Octreotate Increases Tumor Response in Human Small-Intestine Neuroendocrine GOT1 Tumor Model. Cancers, 14(1), 235.

II. Elvborn, M., Rassol, N., Pettersson, D., Shubbar, E., Spetz, J., Helou, K., Forssell-Aronsson, E. *Biological effects in regrown tumors in GOT1 mouse model after hyperfractionated $^{177}$Lu-octreotate treatment.* Manuscript.

III. Elvborn, M., Rassol, N., Pettersson, D., Spetz, J., Shubbar, E., Helou, K., Forssell-Aronsson, E.. Biodistribution and early effects after hyperfractionated administration of $^{177}$Lu-octreotate in GOT1 tumor-bearing mice. Manuscript.

IV. Elvborn, M., Rassol, N., Pettersson, D., Shubbar, E., Spetz, J., Helou, K., Forssell-Aronsson, E..*Late apoptotic effects after treatment with $^{177}$Lu-octreotate in small-intestine neuroendocrine GOT1 tumor model.* Submitted manuscript.

**SAHLGRENSKA AKADEMIN**
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# Improvement of $^{177}$Lu-octreotate treatment of small-intestine neuroendocrine tumors by hyperfractionation

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## Abstract

Neuroendocrine tumor incidence is steadily rising, and the late diagnosis often results in metastatic disease and current treatments mostly prolong life and increase quality of life without increasing cure rate. $^{177}$Lu-octreotate was recently approved for treatment of neuroendocrine tumors, but the dosage scheme should be optimized. The aim of this thesis was to study the effects of fractionated administration of $^{177}$Lu-octreotate in the human GOT1 tumor mouse model.

GOT1 bearing mice were given $^{177}$Lu-octreotate as a single or fractionated administration. The biodistribution and tumor volume response was followed with time. DNA and RNA were extracted from tumor tissue. DNA methylation was evaluated, and expression of genes involved in apoptosis determined.

Hyperfractionated administration gave a more pronounced anti-tumoral effect and longer progression-free survival than single administration with the same total amount of $^{177}$Lu-octreotate. The methylation analysis of genes and promoters revealed $^{177}$Lu-octreotate treatment specific responses across the groups. Altered expression of apoptosis related genes in regrown tumors was modest, with varying commonalities between the groups. Hyperfractionation generally resulted in a different apoptotic gene expression pattern compared with single-administration in regrown tumors. Hyperfractionation led to higher absorbed dose to tumor and lower to kidneys than single-administration. Expression of genes related to apoptosis in tumors were similar between groups early after high dose level of $^{177}$Lu-octreotate, but sometimes with a trend towards higher gene regulation for the hyperfractionated groups. The pro apoptotic genes *BAX*, *FAS*, *GADD45A* and *TNFRSF10B* were significantly regulated at several early time-points for both high dose groups.

In conclusion, hyperfractionation of $^{177}$Lu-octreotate shows promise compared with single administration, and should be tested clinically.

**Keywords**: Peptide receptor radionuclide therapy, PRRT, somatostatin receptor, SSTR, apoptosis, gene expression, epigenetic effects

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