

# Targeted radionuclide therapy for patients with neuroendocrine tumours

## with focus on normal tissue response in $^{177}\text{Lu}$ -DOTATATE treatment

**Johanna Svensson**

Department of Oncology, Institute of Clinical Sciences  
Sahlgrenska Academy at University of Gothenburg  
Göteborg, Sweden

### ABSTRACT

Targeted radionuclide therapy with  $^{177}\text{Lu}$ -DOTATATE for patients with neuroendocrine tumours utilises the frequent overexpressing of somatostatin receptors on the tumour cells. This treatment modality has demonstrated valuable patient benefits and is well tolerated. However, renal and bone marrow toxicity can become dose limiting and persisting. The aim of this thesis was to investigate normal tissue response during  $^{177}\text{Lu}$ -DOTATATE treatment, with focus on kidneys, bone marrow and also the spleen, the organ that receives the highest absorbed dose. To enable analysis of bone marrow response to absorbed dose, a novel image-based method for bone marrow dosimetry was developed.

The first paper included, was a pre-clinical study of morphological and biochemical renal changes in nude mice injected with  $^{177}\text{Lu}$ -, or  $^{90}\text{Y}$ -DOTATATE. The remaining three studies evaluated 51 patients with neuroendocrine tumours, treated with  $^{177}\text{Lu}$ -DOTATATE at Sahlgrenska University Hospital. Patient renal and bone marrow function was evaluated and dosimetry was performed for kidneys, bone marrow and spleen utilising planar and SPECT images acquired after infusion, and the developed automated segmentation method for bone marrow dosimetry.

Selective morphological changes were quantified in renal cortex of nude mice, and corresponding biochemical changes observed, after  $^{177}\text{Lu}$ -DOTATATE injection. These appeared in a dose-dependent manner. No morphological changes were observed for the animals receiving  $^{90}\text{Y}$ -DOTATATE. In the clinical studies, it was found that patients with inferior renal function were exposed to higher mean absorbed renal doses, and experienced enhanced haematological toxicity. It was also shown that a longer residence time for  $^{177}\text{Lu}$  and a higher tumour burden increased the haematological toxicity. A novel image-based method for bone marrow dosimetry was developed, and correlations were found between mean and total absorbed bone marrow doses, and haematological toxicity. The role of the spleen for haematological toxicity was also analysed, and it was observed that radiation exposure of the spleen had an impact on the haematological response. The results in this thesis emphasise that several parameters affects normal tissue response in  $^{177}\text{Lu}$ -DOTATATE treatment. Hopefully, a better understanding of what decides the individual response, may contribute to individualised treatment decisions in the future.

**Keywords:** radionuclide therapy,  $^{177}\text{Lu}$ -DOTATATE, neuroendocrine tumours, normal tissue response, dosimetry

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Akademisk avhandling

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av

**Johanna Svensson**

Fakultetsopponent:

Professor Flavio Forrer

Klinik für Radiologie und Nuklearmedizin

Kantonsspital St Gallen, Schweiz

Avhandlingen baseras på följande arbeten:

- I.* Svensson, J, Mölne, J, Forssell-Aronsson, E, Konijnenberg, M, Bernhardt, P. Nephrotoxicity profiles and threshold dose values for  $^{177}\text{Lu}$ -DOTATATE in nude mice.  
*Nuclear Medicine and Biology 2012;59:756-762*
- II.* Svensson, J, Berg, G, Wängberg, B, Larsson, M, Forssell-Aronsson, E, Bernhardt, P. Renal function affects absorbed dose to the kidneys and haematological toxicity during  $^{177}\text{Lu}$ -DOTATATE treatment.  
*European Journal of Nuclear Medicine and Molecular Imaging 2015;42:947-955*
- III.* Svensson, J, Magnander, T, Hagmarker, L, Hemmingsson, J, Wängberg, B, Bernhardt, P. A novel planar image-based method for bone marrow dosimetry in  $^{177}\text{Lu}$ -DOTATATE treatment correlates with haematological toxicity.  
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- IV.* Svensson, J, Hagmarker, L, Magnander, T, Wängberg, B, Bernhardt, P. Radiation exposure of the spleen in  $^{177}\text{Lu}$ -DOTATATE treatment and its relation to haematological toxicity and volume reduction of the spleen.  
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