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Small-scale dosimetry methods for normal tissues after radioembolization and peptide receptor radionuclide therapy - a focus on the liver parenchyma and bone marrow

Jens Hemmingsson
Avdelningen för Medicinsk strålningsvetenskap, Institutionen för kliniska vetenskaper, Sahlgrenska akademin, Göteborgs universitet

Abstract
Radionuclide therapies are increasingly used in cancer treatments as they have been proven to be both effective and safe. As biodistributions and uptake vary widely between patients, a standardized approach may overtreat or undertreat some patients. Dosimetry-based evidence suggests patient-specific treatment regimens could be improved, as critical organ dose limits are not always reached. This thesis investigated two radionuclide therapies with different targeting mechanisms and their absorbed dose distributions in tumor tissue and liver parenchyma after radioembolization, and in radiosensitive red marrow after peptide receptor radionuclide therapy (PRRT).

In the first study, a patient with hepatocellular carcinoma underwent yttrium-90 radioembolization prior to resection. The dosimetry analysis revealed a low absorbed dose and a small coefficient of variation in the liver parenchyma. However, the distribution in the tumor showed high levels of heterogeneity, with the greatest accumulation of microspheres found in viable tumor tissue. The three consecutive studies (II-IV) focused on the absorbed dose to the red marrow after PRRT. Using an existing bone marrow model, Study II investigated terbium-161, which emits low-energy electrons and may be suited to treat disseminated disease. Results showed high dependence on source distribution and an increased absorbed dose to the red marrow compared to lutetium-177. The third study investigated the presence of somatostatin receptor subtype 2 (SSTR2) on $CD34^+$ stem cells in the bone marrow. A compartment model was used to separate the contribution from blood-based activity and demonstrated prolonged retention in the bone marrow cavities for all patients and skeletal sites. These results inspired the development of a small-scale dosimetry model of the bone marrow in the fourth study to investigate how $CD34^+$ stem and progenitor cells are irradiated by uptake related to the expression of SSTR2. The model utilized previously described spatial distributions of $CD34^+$ stem and progenitor cells to demonstrate an increased absorbed dose from terbium-161 compared to lutetium-177.

In conclusion, our results help to explain the observed hematological toxicities after [^{177}Lu]Lu-DOTATATE therapy by demonstrating a specific uptake in the radiosensitive bone marrow. As upcoming clinical trials with terbium-161 may result in a shift from lutetium-177 in somatostatin receptor-based radionuclide therapies, we used these findings to show that this can lead to increased irradiation of the red marrow.

Keywords: Dosimetry, PRRT, Bone marrow, SSTR2, radioembolization

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I. Jens Hemmingsson, Jonas Högberg, Johan Mölne, Johanna Svensson, Peter Gjertsson, Magnus Rizell, Olof Henrikson, Peter Bernhardt
Autoradiography and biopsy measurements of a resected hepatocellular carcinoma treated with 90 yttrium radioembolization demonstrate large absorbed dose heterogeneities.
Advances in Radiation Oncology 2018 Vol.3 Issue 3 Pages: 439-446

II. Jens Hemmingsson, Johanna Svensson, Nicholas P van der Meulen, Cristina Müller, Peter Bernhardt
Active bone marrow S-values for the low-energy electron emitter terbium-161 compared to S-values for lutetium-177 and yttrium-90.
EJNMMI Physics 2022 Vol.9 Issue 1 No: 65

III. Jens Hemmingsson, Johanna Svensson, Andreas Hallqvist, Katja Smits, Viktor Johanson, Peter Bernhardt
Specific uptake in the bone marrow causes high absorbed red marrow doses during [^{177}Lu]Lu-DOTATATE treatment.
Accepted in the Journal of Nuclear Medicine, May 3, 2023

IV. Jens Hemmingsson, Johanna Svensson, Andreas Hallqvist, Viktor Johanson, Johan Mölne, Nicholas P van der Muelen, Cristina Müller, Peter Bernhardt
Bone marrow dosimetry model for receptor-based radiotherapies; comparison between lutetium-177 and terbium-161.
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