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Treatment planning options for ^{177}Lu-DOTA, Tyr^3-octreotate; verification of therapeutic dose-responses in an animal model

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Abstract

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Objectives: Radionuclide therapy with ^{177}Lu-labelled DOTA,Tyr^3-octreotate (^{177}Lu-TATE) forms an excellent treatment for metastasized somatostatin receptor-over-expressing neuroendocrine tumours. Patient-specific treatment planning might optimize the effectiveness of this therapy even further when aimed at delivering high-absorbed doses to the tumour lesions relative to non-toxic absorbed doses to normal organs. The radiobiology of dose-responses at various dose rates is described by the linear quadratic (LQ) model, with most knowledge originating from external beam radiotherapy. The main subjects of this study comprised the influence of fractionation of ^{177}Lu-TATE therapy on tumour dose-response effects as well as variations in dose rate. Tumour volume over time was used as readout to verify the usefulness of the LQ-model for prospective treatment planning in peptide radionuclide therapy. **Materials&Methods** Experiments were performed in H69 tumour-bearing nude mice. The therapeutic impact of three molar activities of ^{177}Lu-TATE was studied after a single dose and after fractionation of the same dose in multiple administrations. Tumour volume responses over time were compared with response models based on the LQ-model. The kinetic tumour response model is described by coupled differential equations including repair of sub-lethal DNA damage, absorbed dose response according to the LQ-model, and clearance of dead cells during the dose delivery by ^{177}Lu. **Results** Increase in molar activity led to an increase in absorbed dose to the tumours, which led to an increase in median survival (numerical results in table). Splitting the therapy (2x15 MBq) lead to similar anti-tumor therapy effects as single exposure (30 MBq) therapy. Doubling the therapy (2 x 30 MBq) led to an additional 21 day survival period, comparable to the survival gain after single exposure (30 MBq) therapy. All tumour volume curves could be modelled with the kinetic tumour response model using the following LQ-model parameters: α=0.14±0.03 Gy-1 and β=0, clearance of non-dividing cells proceeded with a median half-life of 3.5 days (see Figure). **Discussion** It is possible to generate a predictive model for absorbed dose-effects to tumour volume after ^{177}Lu-TATE therapy. The model follows the fundamental mechanisms of radiation damage and cell response and is therefore a useful instrument for translation of dose-effect relations from mice to humans. Repair of sub-lethal damage was complete, which leads to a negligible quadratic component in the LQ-model. The linear LQ-model parameter was lower than the reference value for H69 tumours. This could be explained by assuming a level of heterogeneity, either in response or in dose distribution.**Conclusion** A tumour response model has been adapted that enables prediction of anti-tumour responses based on absorbed dose, tumour growth and radiation sensitivity. Prospective treatment planning for clinical radionuclide therapies is feasible using this model when all relevant tumour radiobiology parameters are known. This model is a valuable tool to derive these from pre-clinical therapy experiments.

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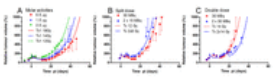
Table 1. H69 tumour bearing mice survival, growth and radiation sensitivity in 177Lu-Tate therapy



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