

# I131-MIBG treatment revisited: How important is scheduling when combined with external beam irradiation?

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## Abstract

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**Objectives** Neuroblastoma is the most frequent extra-cranial tumour in younger childhood. The current treatment of high-risk (stage 4) inoperable neuroblastoma includes a combination of chemotherapy and/or total irradiation with either autologous bone marrow transplantation or peripheral blood stem cell reinfusion. Despite these treatments the 4-year overall survival for high-stage neuroblastoma is still low (69%). Targeted/molecular radiotherapy (MRT) where the overexpressed noradrenaline transporter is targeted with <sup>131</sup>I-MIBG (Meta-iodobenzylguanidine) an analogue of noradrenaline is an effective treatment for relapsed or refractory neuroblastoma. The aim of this study is to investigate whether in vivo imaging could be used to inform scheduling of MRT with <sup>131</sup>I-MIBG in a human neuroblastoma xenograft model (SK-N-SH) to optimize and enhance the efficacy of external beam irradiation (EBRT).

**Methods** To assess the effect of combined EBRT and MRT, a SK-N-SH cancer xenograft model in nude mice was developed. Vessel permeability was evaluated with dynamic, contrast-enhanced MRI (DCE-MRI) to optimize scheduling of MRT (20 MBq) after an initial EBRT (5 Gy - SARRP irradiator) treatment. A subsequent EBRT dose (5 Gy) was delivered to simulate a fractionation scheme combining EBRT and MRT. Survival (as time needed to obtain a set limit tumour volume) was assessed and tumour volumes were determined at different times with MRI.

**Results** DCE-MRI showed an increase in vessel permeability at 24h but not at 72h after EBRT treatment, and resulted in MRT being delivered 1 day after EBRT. Tumour growth was rapid in the control group and these animals were euthanized within 7 days. <sup>131</sup>I-MIBG caused a significant delay in the growth rate of the tumours in comparison to the control group ( $p < 0.01$ ) and the tumours were observed to shrink during the initial 5 days after dosing. However a recurrence was observed at day 7. More interestingly, EBRT treatment 1 day before or 1 week after MRT treatment significantly decreased the tumour volume (from 500mm<sup>3</sup> at day 0 to 40mm<sup>3</sup> at day 7;  $p < 0.001$  vs control and MRT alone group) and increased the overall survival.

**Conclusions** This study demonstrated that the combination of EBRT and MRT potentiated the therapeutic effect in a neuroblastoma model and confirmed that MRI could be used to monitor this effect. Furthermore it emphasized the importance of scheduling the combined treatment according to pathophysiological criteria such as vessel permeability.