

# CHARACTERIZING AND MODULATING THE EFFECTS OF IONIZING RADIATION TO THE JUVENILE HIPPOCAMPUS

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien vid Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinargatan 3, fredagen den 23 maj 2014 kl 9.00

av

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Avhandlingen baseras på följande delarbeten:

- I. Blomstrand M, Holmberg E, Åberg M A I, Lundell M, Björk-Eriksson T, Karlsson P and Blomgren K. **No clinically relevant effect on cognitive outcomes after low-dose radiation to the infant brain: a population-based cohort study in Sweden.** *Acta Oncologica (2014) Early Online:1-8.*
- II. Blomstrand M, Kalm M, Grandér R, Björk-Eriksson T and Blomgren K. **Different reactions to irradiation in the juvenile and adult hippocampus.** *Submitted manuscript*
- III. Blomstrand M\*, Brodin P N\*, Munck af Rosenschöld P, Vogelius I R, Sánchez Merino G, Kiil-Berthlesen A, Blomgren K, Lannering B, Bentzen S M and Björk-Eriksson T. **Estimated clinical benefit of protecting neurogenesis in the developing brain during radiation therapy for pediatric medulloblastoma.** *Neuro-Oncology (2012) 14(7):882-889*
- IV. Brodin P N, Munck af Rosenschöld P, Blomstrand M, Kiil-Berthlesen A, Hollensen C, Vogelius I R, Lannering B, Bentzen S M and Björk-Eriksson T. **Hippocampal sparing radiotherapy for pediatric medulloblastoma: impact of treatment margins and treatment technique.** *Neuro-Oncology (2014) 16(4):594-602*

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# CHARACTERIZING AND MODULATING THE EFFECTS OF IONIZING RADIATION TO THE JUVENILE HIPPOCAMPUS

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## ABSTRACT

Survival rates after childhood cancer treatment have improved, leading to a growing population of survivors. Radiotherapy is an important tool for curing cancer in the brain. Unfortunately, radiotherapy is associated with late side effects e.g. of cognitive impairment. The mechanisms underlying radiation-induced cognitive dysfunctions are not fully understood but involve changes in the neurogenic niche of the hippocampus. The aim of this thesis was to characterize and modulate the effects of ionizing radiation to the hippocampus of the juvenile brain, with the future goal of ameliorating cognitive deficit of childhood cancer survivors following radiation for intracranial disease.

We investigated the effects of low-dose radiation of the brain in infancy. A total of 3,860 boys were treated with radiation for cutaneous hemangiomas before the age of 18 months. Of these, 3,030 were analyzed for military test scores at the age of 18 years and 2,559 for the highest obtained educational level. We also characterized and compared the radiation-induced reactions in the hippocampus of the juvenile and adult rat brain, as well as evaluated the modulating effect of amifostine, WR-1065 and N-acetylcysteine during cranial irradiation of the juvenile rat brain. This was done in a rat model. Further, we tried to modulate the dose to the hippocampus in medulloblastoma patients by the use of modern radiotherapy techniques. Different radiation prescription scenarios, by means of computer-based treatment, were used to evaluate the possibilities of sparing the hippocampus from radiation and to assess their potential benefits regarding cognitive outcome.

We did not find any effect on the highest obtained education when we investigated the risk of cognitive dysfunctions after exposure to low doses of cranial radiation in infancy. There was no decrease in logical, technical or spatial test scores after radiation doses up to the highest dose category (median 680 mGy). Verbal test scores displayed a very small but statistically significant trend for decreasing scores with increasing doses to the hippocampus. We concluded that the juvenile brain, from a clinical perspective, was not sensitive to doses overlapping the range used for diagnostic purposes, contrasting with earlier findings. For therapeutic doses of radiation in rodents, we found that the radiation reaction in the hippocampus differed in the juvenile brain compared to the adult brain in terms of density of resident microglia, number of activated microglia, levels of apoptosis, specific cytokines/chemokines and growth factors. In rodents, we did not find any protection by amifostine, WR-1065 or N-acetylcystein using tolerable doses during cranial radiation. However, in children we could conclude that sparing the hippocampus from radiation during cranial radiotherapy is feasible by the use of modern treatment techniques. We found that the greatest potential for hippocampal sparing was offered by intensity-modulated proton therapy. Interestingly, we also found that the use of different techniques influenced the dose to the hippocampus to a higher extent, than the use of smaller treatment volumes for the tumor boost. Further, we estimated that a hippocampal sparing strategy could ameliorate the cognitive impairment seen after cranial radiotherapy.

**Keywords:** low-dose radiation, CNS, hippocampus, apoptosis, cytokines, growth factors, microglia, medulloblastoma, hippocampal sparing, tumor bed boost, cognitive risk estimation

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