BRAIN TUMORS IN CHILDREN

INTERVENING WITH THE AFTERMATH: RELAPSE AND LONG TERM SIDE EFFECTS

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i föreläsningssal Tallen, Drottning Silvias barn- och ungdomssjukhus, den 17 maj, klockan 9.00

av

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Avhandlingen baseras på följande delarbeten:

I. Sabel M, Fleischhack G, Tippelt S, Gustafsson G, Doz F, Kortmann R, Massimino M, Navajas A, von Hoff K, Rutkowski S, Warmuth-Metz M, Clifford S C, Pietsch T, Pizer B, Lannering B. **Relapse patterns and outcome after relapse in standard risk medulloblastoma: a report from the HIT-SIOP-PNET4 study** *J. Neurooncol.* 2016;129(3):515-524.

II. Sabel M, Sjölund A, Broeren J, Arvidsson D, Saury J. M, Blomgren K, Lannering B, Emanuelson I. **Active video gaming improves body coordination in survivors of childhood brain tumours** *Disabil Rehabil*. 2016;38 (21):2073–2084.

III. Sabel M, Sjölund A, Broeren J, Arvidsson D, Saury J-M, Gillenstrand J, Emanuelson I, Blomgren K, Lannering B **Effects of physically active video gaming on cognition and activities of daily living in childhood brain tumor survivors: a randomized pilot study** *Neuro-Oncology Practice* Epub August 29, 2016; DOI: 10.1093/nop/npw020

IV. Sabel M, Kalm M, Björk-Eriksson T, Lannering B, Blomgren K. **Hypothermia after cranial irradiation protects neural progenitor cells in the subventricular zone but not in the hippocampus** *International Journal of Radiation Biology*, accepted for publication April 13, 2017. DOI:10.1080/09553002.2017.1321810

SAHLGRENSKA AKADEMIN
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Abstract

After completing primary treatment, childhood brain tumor patients enter a follow-up phase. Follow-up is needed for two main reasons; to detect relapse and to diagnose late side effects. The aims of this thesis were; 1) To describe and analyze the pattern of relapse after treatment for medulloblastoma – the most common malignant brain tumor in childhood – with the aim to find potentially successful relapse treatment and; 2) To investigate ways to lessen the side effects of brain tumor treatment, especially the cognitive side effects.

Methods: Long-term outcome of 338 medulloblastoma patients enrolled in the HIT-SIOP-PNET4 trial was investigated, with a focus on relapse diagnosis, pattern of relapse, and treatment of relapse. In a separate randomized, single-center, single-blinded, pseudo crossover study, the potential benefit of physically active video gaming in childhood brain tumor survivors was investigated. Thirteen children, all previously treated with cranial radiotherapy, were randomized to either active video gaming (with weekly internet-based coaching sessions) followed by a waiting list period, or these periods in reverse order. They were assessed before and after each period, with measures of cognition, motor function and activities of daily living (ADL). Finally, in a rodent model the potentially protective effect of post-irradiation hypothermia on the neurogenic areas of the brain – the subventricular zone (SVZ) and the granule cell layer (GCL) of the hippocampus – was examined. Young rats were randomized to either normothermia or hypothermia for eight hours post-irradiation, or a control group. Their brains were examined one week later, measuring the SVZ and GCL areas and counting the number of proliferating cells and microglia.

Results and conclusions: The ultimately grim prognosis for patients with recurrent medulloblastoma, irrespective of treatment, is confirmed. Surgery for histological diagnosis and research should be encouraged, and can in selected cases prolong survival, but new treatment options are needed. Active video gaming improves body coordination and the execution of ADL. Positive effects on cognition is a possibility, although not confirmed in this pilot study. Hypothermia after irradiation of the brain has a protective effect on the SVZ, but not the GCL, one week post-irradiation. The long-term and functional effect of this finding needs further exploration, together with studies of the effect of hypothermia on brain tumors.

Keywords: medulloblastoma, relapse, radiotherapy, cognition, exercise therapy, video games, hypothermia, pediatric, brain tumor

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