1241 POSTER

Risk estimation of radiation-induced thyroid cancer in children undergoing prophylactic cranial irradiation with photons 6 MV – A Monte Carlo study

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Background: To estimate the risk of thyroid cancer induction resulting from prophylactic cranial irradiation in children with acute lymphoblastic leukemia.
Material and methods: The MCNP (4C2) Monte Carlo code was used to simulate a 6 MV linear accelerator photon beam (Philips/Elekta SL75/5). Mathematical anthropomorphic phantoms generated by BodyBuilder software (White Rock Science, White Rock, NM, USA) to simulate the average individuals of 3, 5, 10 and 15 years old, were used. Prophylactic cranial irradiation was modeled with two lateral and opposed fields at 100 cm source-to-skin distance. For each patient age, lead blocks shielding facial structures and eye globes, on a Lucite tray, were modeled. The mean radiation dose to thyroid gland was calculated. Additionally, a 10-cm-thick lead block on the patient couch, to protect the thyroid gland, was simulated by MCNP code and the mean radiation dose to shielded thyroid gland was determined. The risk for thyroid cancer induction was assessed using appropriate risk coefficient.
Results: The percentage thyroid dose was found to vary with respect to child age. For a child of 3, 5, 10 or 15 years old, the percentage thyroid doses were 4.4, 4.0, 3.45 and 2.85%, respectively. For a treatment course delivering 20 Gy to tumor, thyroid dose varies from 57.6 to 88.0 cGy depending on child age. The consequent excess relative risk of thyroid cancer induction was found to be 6.8, 6.2, 5.3 and 4.4 for a child of 3, 5, 10 and 15 years old, respectively. The use of a couch block reduced the thyroid dose and the consequent excess relative risk by 40 to 62%, depending on child age.
Conclusions: Prophylactic cranial irradiation in children can result in an increased risk for thyroid cancer induction. The use of the appropriate thyroid shielding can considerably reduce (40 to 62%) the risk for carcinogenesis.

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Negative prognostic factors in childhood ALL – the experience of a single Romanian center

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Background: The prognostic and evolution of ALL in children has become increasingly better during the last decade. Still, in our center, the cohort of patients submitted to standardized treatment, reached a 5 year event free survival (5yEFS) of only 52%. Observing that our results do not measure up to those found in the literature, we proceeded to analyze the causes that led to our results.
Material and method: The study was conducted on 156 patients with ALL diagnosed and treated according to BFM 1990 and 1995 in our center in the period of 1990–1998. We analyzed the demographic data: sex, ethnic group, age, clinical and biological (Hb, L, FAB type, karyotype, immunophenotype, and molecular biology) data at the onset of disease, response to treatment, and the 3 and 5 year EFS.
Results: Forty-three percent of our patients were over 6 years old, while 15.3 were under 2y.o. Male to female ratio was 1.29. Twelve percent of them belonged to the rroma ethnic group. CNS involvement at onset was present in 3.84% of patients, while mediastinal tumor was found in 0.64% of them. The onset values of leukocytes (L) and hemoglobin (Hb) were assessed as follows: 16.3% of patients had >50,000/mm^3; 5yEFS was 57% in patients with L>50,000/mm^3 and 78% in those with L<20,000/mm^3; Hb >8 g/dl was found in 34% of patients; 5yEFS was 50% in patients with Hb>10 g/dl and 75% in those with Hb<8 g/dl ($p = 0.0006$); FAB type L2 was present in 17%of patients while L3 was demonstrated in 3.2% of them. Immunophenotype T was found in 3.2% of patients; CD10 was negative in 10.5%. Quantitative cytogenetic anomalies were found in 54% patients while qualitative anomalies were present in 16%. Molecular biology (PCR) studied in 35.89% of our patients revealed rearrangements in 27% of them (MLL-AF4 – 2.56%; BCR-ABL – 1.28%). Positive response to corticosteroids influenced the overall survival, with 5yEFS of 79%, while resistance to corticotherapy led to 31% 5yEFS ($p = 0.0023$). Lack of compliance to treatment understood as exclusion of 1 drug was faced in 19.87% cases, reduction of doses in 8.97%, delay in administration of drugs in 47.43%. Stop or refusal of therapy had a deleterious impact on the long term survival in 4.48% of our patients. CNS prophylaxis was not administered in 32% of cases.
Conclusions: When compared to the literature our results are worse due to the particularities of the studied cohort: increased percent of patients older than 6 years and under 2 years of age, increased proportion of patients with FAB L3 and CALLA negative patients, hyperdiploid status in 26.3% patients. However, the most important factor for negative prognostic was lack of compliance to treatment. We presume better results in the group of patients treated during 1998–2005.

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Late effects of CNS prophylactic treatment in childhood due to ALL using Magnetic Resonance Spectroscopy (H-MRS)

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Purpose: The aim of this study was to evaluate changes in magnetic resonance imaging (MRI) and magnetic resonace spectroscopy (MRS) of the brain in survivors with ALL to assess neurotoxicity follow prophylactic treatment including cranial irradiation and/or intrathecal administration of methotrexate.
Methods: The study was performed including two groups of patients. The first group-30 children had been irradiated and received intrathecal methotrexate and second group consisted of 15 children treated with intrathecal metotrexate without radiotherapy. Radiotherapy was performed using fraction dose 1.8 Gy up to total dose of 18 Gy. MTX chemotherapy doses depended on risk group.
Results: MRI of brain was abnormal in 13(43%) cases in group with cranial irradiation and intrathecal chemotherapy. We observed significant changes in H-MRS metabolite ratios even in patients without changes on imaging. We didn't observe changes on imaging and only one child had altered metabolism observed by MRS in group of patients without radiotherapy.
Conclusions: The MRS could be a valuable method to assess brain tissue metabolism after radiotherapy. That method may be recommended for children with ALL to observe neurotoxicity of prophylactic irradiation.

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Antiangiogenic therapy in high risk medulloblastoma: the role of microarray analysis

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It is noteworthy that a characteristic of posterior fossa tumors is high level of neovascolarization. Studies showed this process is supported by bFGF, VEGF and PGE2 high level expression. A major focus in high risk medulloblastoma is identifying molecular targets, as growth factors, COX2 and microvessel density that can be used for an antiangiogenetic therapy. Expression profiling of medulloblastoma by microarray analysis can be used to identify the genes implied in neovascularization process, thereby revealing new targets for therapy.
The authors determined the molecular profiling in liquor cell samples of five medulloblastoma relapses by microarray analysis. The patients underwent surgical treatment of primary tumor followed chemotherapy before and after radiotherapy and stem cell reinfusion at the end of treatment according to a high risk medulloblastoma protocol. After few months the patients relapsed and at this time an anti-angiogenetic/anti-tumor program was proposed after ethical consensus. The antiangiogenic therapy included continuous oral administration of thalidomide to suppress the VEGF and bFGF-induced neovascularization and celecoxib to inhibit the COX-2 dependent endothelial cell activation. The microarray analysis was performed as previously described (Eisen et al. Methods Enzymol, 1999; 303:179–205). The analysis was performed using microchips that include 1000 cDNAs. Images were analyzed with GenPix Pro 4.1 software (Axon Instruments, Foster City, CA), and fluorescence ratios was calculated. Moreover, the tumor neoangiogenesis was also characterized by determination of microvessel density and COX2 immunoistochemistry.
Several overexpressed genes were identified and considered for possible targets of specific anti-angiogenetic therapy. All patients showed good levels of expression in all the factors involved in the neo-vascularization

process such as VEGF, bFGF, COX 2, and a relatively high level of DNA topoisomerase II a therapeutic target of etoposide. All microrarray experiments were repeated twice. The high levels of growth factors and COX2 mRNAs were confirmed by immunoistochemistry analysis. On the basis of these results we preceded to antiangiogenetic approach. At this time after few months of follow up the instrumental examinations confirmed a disease stabilization in three patients, a light regression in a patient, while the rapid and extensive progression of the disease caused the death of a child after a month of antiangiogenetic therapy.
Thus, we showed that the gene expression monitoring could provide new insight into many aspects of posterior fossa tumors as revealing targets for antiangiogenetic therapy. New drug development and evaluation will likely be accelerated both through the identification of novel molecular targets and through the selection of patients for clinical trials with specific tumor gene expression profile.

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Experience with treatment of lymphocyte predominance Hodgkin's disease in children

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Background: We retrospectively evaluate clinical characteristics and outcome in children with nodular lymphocyte predominant Hodgkin disease (LPHD), which is a rare entity characterized by neoplastic popcorn cells CD 20+, CD 30−, CD 15−, EMA+, Bc 16+ within nodular background composed of small B lymphocytes.
Material and methods: From January 1996 to December 2004, 155 children and adolescents with Hodgkin disease were treated in the Department of Paediatric Hematology and Oncology of the Faculty Hospital Motol in Prague. Nodular lymphocyte predominant Hodgkin disease was histologically confirmed in 7 children (4.5%) – 6 boys, 1 girl. The age range was 7–17 years (mean of 14.9 years). Initial staging included complete physical examination, blood studies and imaging studies as X rays, CT scans and 4 patients (57%) had PET scan. Disease presentation was localized in 5 patients (71%) and advanced in two patients (29%) – both Stage III. Only one patient presented with B symptoms and one patient had bulky disease. Neck was the common site of involvement (5 patients). All patients were treated with chemotherapy combined with involved field radiotherapy. Chemotherapy treatment was not uniform – 3 patients received 5 cycles DBVE-PC (doxorubicin, bleomycin, vinkristine, etoposid, prednisone, cyclofosfamide), two patients received 2 cycles DBVE, one patient 4 cycles DBVE due to partial response after the first two cycles and one was treated with 4 cycles ABVD/COPP. Involved field radiation therapy was administered to all patiens in dose 21–25.5 Gy.
Results: All patients achieved complete remission after combined modality treatment. At a median follow up of 3.2 years (range 2.2 to 9 years) 2 patients relapsed (29%). Both relapses were more than 1 year after primary diagnosis (20 and 28 months) and both patients achieved second complete remission.
Conclusion: Current strategy of treatment LPHD is aimed at high cure rates with less toxic regimens to limit risk of late complications and secondary malignancies. But careful long term follow-up is essential for risk of late relapses.
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Phase II study of Gemcitabine in children with solid tumors of mesenchymal and embryonal origin

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Background: Gemcitabine inhibits DNA synthesis and repair and shows efficacy in many types of adult malignancies, including previously untreatable pancreatic cancer. No data are available about its effectiveness in children. To determine the efficacy of gemcitabine the drug was administred by i.v. short term infusion over 30 min at a dose of 1200 mg/m^2 weekly for 3 weeks in children with first or subsequent recurrence of a solid tumor of embryonic or mesenchymal origin if standard therapy failed to offer any curative therapeutic option.
Results: From May 2003 to April 2005, 14 male and 6 female patients at the median age of 15.8 years (2–23) were recruited for the prospective open-label multicenter phase II study of gemcitabine in Germany and Austria. The patients suffered from soft tissue sarcoma (n = 8), Ewing's sarcoma (n = 4), Neuroblastoma (n = 3), Hepatoblastoma (n = 2), Osteosarcoma (n = 2) or Nephroblastoma (n = 1). Mean duration of therapy was 31.4 days (7–99), equalling 4.6 (2–11) courses of gemcitabine. 2 patients, whose "Best Overall Response" according to RECIST-criteria (i.e. minimal 6 courses) was evaluable, had stable disease documented for 69 and 70 days, respectively (neuroblastoma, Ewing's sarcoma), whereas no response to gemcitabine was documented. The other patients left the trial mainly due to early progress. The mean dosage per course was 1104 mg/m^2. In 33/88 evaluable courses dosage had to be reduced or omitted for grade 3–4 haematologic toxicity. No suspected unexpected serious adverse reactions (SUSAR's) were reported.
Conclusions: Gemcitabine at the dose and schedule of this trial was not effective for children with refractory solid tumors. Given the variety of other promising agents, further evaluation of gemcitabine as single treatment of childhood solid tumors does not appear to be warranted. Nevertheless, publishing of negative results is indispensable for diminishing the Publication only bias.

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Alterations of brain metabolism after therapy of paediatric brain tumors. a serial proton magnetic resonance spectroscopy study

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Aim: The aim of the study was to evaluate metabolic changes in tumor bed occurring after therapy of pediatric brain tumors using serial proton magnetic resonance spectroscopy studies.
Material: The examined group consisted of 15 children with brain tumors treated with surgery, chemotherapy and radiotherapy. Eight children had medulloblastomas, four had astrocytomas, one had oligodendroglioma, one glioblastoma and one had a mixed tumor having features of both PNET and glioblastoma.
Methods: Short echo-time (TE 30 ms) point-resolved spectra were acquired using 2 Tesla clinical scanner (Elscint Prestige). The proportions of N-acetylaspartate (NAA), choline (Cho), myo-inositol (mI), lactate (Lac) and lipids (Lip) signal intensities were calculated using creatine (Cr) signal as an internal reference. The spectra were acquired from tumor bed and form unaffected brain tissue of contralateral hemisphere as a comparison. The first examination was made between third and sixth month after therapy, the second 8–12 months after therapy and the third examination was performed approximately 18 months after completion of therapy. The results were compared using t-test for dependent samples.
Results: In all cases there were significant disturbances in brain metabolism detected both in the spectra acquired from the tumor bed and from control area. The most important alterations were decrease of NAA/Cr and increase of Cho/Cr, Lac/Cr and Lip/Cr proportions. The observed changes did not differ significantly between subsequent examinations.
Conclusions: Alterations of brain metabolism after combined therapy of brain tumors in children affect both tumor bed and uninvolved area of brain tissue and are stable in subsequent examinations indicating long-lasting or permanent brain damage.

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Expression profiles of 'minimal residual disease' (MRD) markers for neuroblastoma in peripheral blood and its cell fractions by real-time quantitative PCR (RQ-PCR)

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Background and Aim: In neuroblastoma (NBL) specific and sensitive markers are essential for MRD detection. NBL cells highly express tyrosine hydroxylase (TH), DOPA decarboxylase (DDC), chromogranin-B (CHGB), GD2 synthase (GD2), dopamin beta hydroxylase (DBH), paired-like homeobox 2B (PHOX2B), growth associated protein 43 (GAP43), synaptosomal associated protein (SNAP), stathmin-like 2 (STMN2), stathmin-like 4 (STMN4), and cholinergic receptor (CHRNA3). TH, DDC, GD2 and CHG are among common MRD markers for NBL. In previous experiments, PHOX2B had no expression in normal bone marrow (BM), DDC was expressed in 2/67, and other markers in $\geqslant$ 14/67 samples. In peripheral blood (PB), PHOX2B, DDC, CHRNA3 were negative; TH was positive in 2/22, DBH in 1/22 samples, and others in $\geqslant$ 10/22 of samples.