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Original article

Lung toxicity after radiation in childhood: Results of the International Project on Prospective Analysis of Radiotoxicity in Childhood and Adolescence

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ABSTRACT

Background and purpose: This study presents the evaluation of acute and late toxicities of the lung in children and adolescents after irradiation in terms of dose–volume effects.
Materials and methods: Irradiated children and adolescents in Germany have prospectively been documented since 2001 in the "Registry for the Evaluation of Side-Effects after Radiotherapy in Childhood and Adolescence (RiSK)"; in Sweden since 2008 in the RADTOX registry.
Results: Up to April 2012, 1,392 children were recruited from RiSK, and up to June 2013, 485 from the RADTOX-registry. Of these patients, 295 were irradiated to the lung. Information about acute toxicity was available for 228 patients. 179 patients have been documented concerning late toxicity (≥grade 1: $n = 28$). The acute toxicity rate was noticeably higher in children irradiated with 5–20 Gy ($p < 0.05$). In the univariate analysis, a shorter time until late toxicity was noticeably associated with irradiation with 5–15 Gy ($p < 0.05$).
Conclusion: Acute and late toxicities appear to be correlated with higher irradiation volumes and low doses. Our data indicate that similar to the situation in adult patients, V5, V10, V15 and V20 should be kept as low as possible (e.g., at least V5 < 50%, V10 and V15 < 35% and V20 < 30%) in children and adolescents to lower the risk of toxicity.
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Radiotherapy plays a pivotal role in many multimodal therapy concepts in paediatric oncology [1]. Due to a low cure rate in the past, therapy optimization has long been directed towards the extension of life [2]. The growing number of surviving children who were cured of malignant diseases has resulted in an increased interest in late toxicity after treatment with radiotherapy, surgery and chemotherapy [3]. Changes in irradiation technology and the introduction of new technologies, in addition to improved local surveillance, have contributed to a decrease in late toxicity [4–6]. In Germany, the "Registry of the Evaluation of Side Effects after Radiotherapy in Childhood and Adolescence (RiSK)" was established by the "German Group of Paediatric Radiation Oncology (APRO)", a working group of the "German Society of Radiation Oncology (DEGRO)" and the "German Society of Paediatric Oncology and Haematology (GPOH)" [4,7]. Since 2008, the "International Project on Prospective Analysis of Radiotoxicity in Childhood and Adolescence (IPPARCA)" is a collaboration with the "Swedish Working Group for Paediatric Radiotherapy (SvBRG)". The Swedish registry, named RADTOX, is a web-based registry for children younger than eighteen years who have undergone radiotherapy. Its case report forms (CRFs) are based on the RiSK forms. The aim of these prospective multi-centre registries is to evaluate the radiation dose–effect relationships in organs and parts of organs as a result of combined modality treatment, such as surgery and/or chemotherapy [2,4,8]. This knowledge will help to assess individual treatment risks and facilitate the conception of prospective therapy studies. The feasibility of RiSK has already been proven,

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and initial results were recently published [2–4,7,9]. To date, there have been publications on single organs, including the kidney, thyroid gland and liver [3,7,9]. Furthermore, there has been one publication on the acute toxicity of several organs (including the lung) after the irradiation of children and adolescents [8] and a very recent study on acute toxicity of grades 3 and 4 [10]. The lung is one of the most radiation-sensitive structures in the body, but little is known about late toxicity of the lung after radiotherapy in children and adolescents [11]. Therefore, the aim of this study was to analyse acute and late toxicities in relation to irradiated lung volumes.

Materials and methods

The RiSK and IPPARCA study protocols and the original documentation forms have already been published [1–4,8,12]. Briefly, the RiSK registry started its pilot phase in 2001 at a few centres. It is widespread throughout Germany and has been supported by "The German Childhood Cancer Foundation" since 2004 [2]. In 2008, RiSK and RADTOX established IPPARCA. Standardized parameters have been documented, including the irradiation techniques used, duration, target volume, dose to all organs and dose–volume information for the liver, heart, lungs and kidneys (including the documentation of V5–V60 as the organ volumes exposed to 5–60 Gy, respectively) [8]. The fractionation doses were individually adjusted, with a 10% and 90% quantile of 1.5 Gy and 2.1 Gy per fraction, respectively. A dose of 2 Gy per fraction was applied in 14.3% of all irradiation cases; 1.8 Gy per fraction was applied in 55%. The median overall dose was 19.8 Gy, with a range of 12–60 Gy. Due to clinical relevance, only physical doses were used.

Documentation from local radiotherapists was reviewed and collected at the study centre in Münster [7,12]. In Sweden, a monitoring radiotherapy nurse collected the radiotherapy data available from RADTOX. This analysis includes children and adolescents up to 18 years of age who were irradiated to the whole lung or parts of the lung or underwent total body irradiation (TBI). The parents of the patients in this analysis were informed about the aim of RiSK/RADTOX and gave their consent to providing documentation. RiSK was approved by the Ethics Committee of the University Clinic of Münster, and RADTOX was approved by the Umeå regional ethics committee in Sweden. Measurements of acute toxicity (maximum toxicity, which occurs during treatment or up to 90 days after the end of treatment) and late toxicity of the lung (which occurs more than 90 days after the end of treatment) were performed according to "Radiation Therapy Oncology Group"/"European Organization for Research and Treatment of Cancer" (RTOG/EORTC), published by Cox et al. [13] (Supplementary material 1: Table 1). The applied chemotherapy was categorized as "often" or "very often" pulmotoxic [14] .

Statistical analyses

Statistical analyses were performed using SAS software, version 9.4 of the SAS System for Windows (SAS Institute, Cary, NC, USA) and R 3.4.1 [15]. Inferential statistics were intended to be exploratory, not confirmatory. *P*-values represent a metric measure of evidence against the respective null hypothesis and were used only to generate new hypotheses. Therefore, neither global nor local significance levels were determined, and no adjustment for multiplicity was applied. *P*-values ≤ 0.05 were considered statistically noticeable. Standard univariate statistical analyses were applied. Categorical variables are shown as absolute and relative frequencies. Continuous variables are shown as median [minimum – maximum]. Acute toxicity was analysed as a binary variable (grade 1–4/grade 0). Patients who received total body irradiation were excluded from the calculation of acute toxicity. There was a lack of forms concerning acute toxicity, probably because of the short irradiation time; however, documentation concerning late toxicity was generally available. Patients treated with protons were also excluded (eight patients) because the lack of comparability to patients treated with other radiotherapy techniques. Fisher's exact test was used to quantify the association between acute toxicity and binary categorical variables. The nonparametric Mann–Whitney U test was applied for continuous variables. To determine the prognostic influence on acute toxicity, univariate logistic regressions were performed. The potential influencing variables are listed in Table 1. If the total dose–volumes for the whole lung (V5–V60) were not documented, they were calculated using the mean of the appropriate left and right dose–volumes. The time until late toxicity (at least grade 1) was analysed using time-to-event methods. The Kaplan–Meier estimates, log-rank tests and univariate Cox regression were applied as appropriate [16,17]. Additional multivariate analyses were performed considering the impact of the organ volumes exposed to radiation for acute and late toxicities using logistic regression for acute toxicity (at least grade 1) with independent variables V5–V20 and Cox regression for late toxicity (at least grade 1) with independent variables V5–V15. Due to the small number of events, additional variables were not included. The results are reported as odds ratios (OR) or hazard ratios (HR) with corresponding 95% confidence intervals (95% CI).

An exploratory determination of the most prognostic dose–volume variable (V5–V60) for the development of any acute or late toxicity was performed and an optimal cut-off point based on its prognostic value was determined to divide this variable into two categories. For acute toxicity, ROC analyses were performed. The area under the curve (AUC) and confidence limits were determined to identify the optimal variable. The optimal cut-off value was chosen by maximizing Youden's index [18]. Prognostic variable selection and threshold determination for late toxicity were performed based on the maximally selected two-sample logrank statistics using the R package *maxstat* [19].

Results

In total, 1,392 patients from 62 radiotherapy centres were recruited from the RiSK database up to April 2012. Until January 2014, 485 children were included in the RADTOX registry. In this analysis, 295 children and adolescents underwent irradiation to the lung in Germany (249 children, 31 centres) and Sweden (46 children, six centres). The patient characteristics are presented in Table 1.

In total, 247 forms regarding acute toxicity were available. Nineteen patients received TBI and were excluded from this analysis, leading to 228 evaluable forms regarding acute toxicity. After lung irradiation, 28 patients developed acute toxicity (grade 1: $n = 26$; grade 2: $n = 1$; grade 3: $n = 1$). The patient with acute toxicity grade 3 is described in Supplementary material: Table 2. The patients who developed acute toxicities were noticeably more likely to have pre-existing lung impairment, were more frequently irradiated at higher volumes (5 Gy to $\geq$50% volume, 20 Gy to $\geq$30% volume) or were irradiated with higher median volumes exposed to 5, 10, 15, 20 Gy (V5, V10, V15, V20) than the patients without acute toxicity (Table 2). The boxplots in Fig. 1 show the dose–volumes of irradiation to the lung for patients with and without acute toxicity. Further univariate analyses revealed no statistically noticeable relationship. Additional multivariate analyses were performed for acute toxicity considering the impact of the organ volumes exposed to radiation by using V5–V20 as independent variables in the logistic regression. The covariate-adjusted odds for acute toxicity increased by 1.38 (95% CI: 1.03–1.84) per 10%

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