Late Effects of Abdominal Irradiation in Children: A Review of the Literature

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Abstract. *Aim: To comprehensively summarize the most important literature regarding the late effects of radiotherapy to the abdomen in childhood and adolescence. Materials and Methods: Published trials, studies and series were identified using the PubMed database. The key words late effects, late sequelae, child, radiation, radiotherapy, abdomen, kidney, liver, and bowel were used. Results: A dose–volume effect is confirmed for liver irradiation. Radiation with doses <20 Gy to major parts of the liver or higher doses to smaller parts seems to be safe. Kidney function impairment due to radiation is rare in children. Renal sequelae may occur after radiation to the remaining kidney in patients who underwent nephrectomy or who received higher doses to both kidneys. Several reports describe small bowel obstruction as a sequelae of surgery, but radiotherapy seems to be less important. Conclusion: Several retrospective reports describe radiation-associated late sequelae in children. However, there is still a lack of sufficient data regarding the characterization of dose–volume effects.*

Continuous improvements in multimodal therapy approaches have led to an enormous increase of survival rates to more than 70% in pediatric oncology during the recent decades (1). However, surviving individuals are at risk of developing late effects after their antitumor therapy including surgery, radiation therapy, or chemotherapy (2). Nowadays, many different innovative radiotherapy treatment approaches are used to reduce potential side-effects (3-5). The evaluation and care regarding survivors of malignancies in childhood and adolescence is of major interest (6). Radiotherapy as part of a multimodal treatment approach is an important treatment strategy for many malignancies in pediatric oncology (7). While its benefit has been demonstrated for several tumors, the risk for potential side-effects cannot be reliably quantified due to insufficient data. An overview of the long-term side-effects of radiotherapy in survivors of childhood cancer was published by Dieckmann *et al*. in 2002 (8). However, due to the consideration of all potential organs at risk, detailed information regarding specific sites could not be given. A comprehensive overview of published reports on late sequelae after radiotherapy to the thorax in children and adolescents was recently published (9). The aim of the present review is to comprehensively summarize the most important literature regarding the late effects of radiotherapy to the abdomen in childhood and adolescence, with special emphasis on the late sequelae in the liver, kidneys, and bowel. Data obtained solely from total body irradiation (TBI) are not considered in this review, due to the different multimodal therapy and special situation regarding late effects.

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Materials and Methods

Published trials, studies and series were identified using the PubMed database. The key words late effects, late sequelae, child, radiation, radiotherapy, abdomen, kidney, liver, and bowel were used. Cross-referencing, using the references of all identified studies, helped complement the computer-aided searches. All studies but case reports were included if presented in the English language.

Results

Based on the described search strategy 32 papers were found to be informative for this review. Case reports and papers dealing with adults only were excluded. Further three papers could be identified based on cross-referencing using the references of found studies. Most papers dealing with the long-term toxicity of radiotherapy in pediatric oncology have been published on Wilms' tumor or Hodgkin's disease. Reports of side-effects after radiotherapy for childhood sarcomas or other malignancies are less frequent. Due to their retrospective designs and the lack of three-dimensional radiotherapy treatment planning in former times, most papers do not refer to data regarding radiation doses to organs at risk. In most cases, only data for nominal doses and quite

uncertain field borders were available. A further limitation is the potential interaction with chemotherapy and surgery. In spite of these limitations, several papers report toxicity rates that could be helpful in predicting the range of the organ dose–effect relationships. In the following sections, literature reporting side-effects in abdominal organs after radiotherapy in childhood and adolescence are discussed.

Liver. Radiation-induced liver disease in adults is a well-known phenomenon (10). As early as 1970, Tefft *et al*. (11) described 99 children and adolescents who had received irradiation to part or all of the liver with a follow-up of at least 6 months after radiotherapy (mean: 47 months). Toxicity was evaluated clinically and with liver function tests, peripheral hematological analysis, and/or radioisotope liver scanning. All patients had received chemotherapy (actinomycin D, alkylating agents, or 5-fluorouracil). Radiation was performed in most cases with doses of 25-35 Gy. Abnormal results for clinical liver evaluation were seen in 12% of patients with right lobe irradiation, but only in 2.7% of patients with left lobe irradiation. When all methods of follow-up examination were used, abnormal results were found in 78% of cases after radiotherapy to the right lobe but only 50% of cases after radiotherapy to the left lobe. The comparison of the different doses revealed abnormal follow-up results for 54% of cases with doses <25 Gy, 64% of the cases with doses 25-35 Gy, and 86% of cases with doses >35 Gy. In a later analysis (12), data were presented from 263 patients who had been treated with abdominal radiation for Wilms' tumor (92 right abdomen, 143 left abdomen, 28 whole abdomen) with doses of 18-40 Gy. Fifteen patients (5.7%) developed liver abnormalities, including five patients with severe thrombocytopenia and transient abnormalities of liver function tests. Ten out of these fifteen patients had evidence of clinical liver failure in addition to function test abnormalities, including hepato-splenomegaly, jaundice, and ascites. Recovery from these abnormalities occurred within another 2-4 months in all but three of these patients. The degree of hepatic damage was related to the liver volume irradiated and the dose delivered. This report confirmed earlier findings.

Flentje *et al*. (13) analyzed hepatotoxicity in 58 irradiated nephroblastoma patients during postoperative treatment. Eleven our of these 58 patients (19%) developed signs of hepatotoxicity, all with radiotherapy to major parts of the liver. There was no clear dose response for the dose range involved (30% toxicity <20 Gy *versus* 28% >20 Gy to major parts of the liver). There was also no convincing difference between subtotal and total liver irradiation, but the severity of liver toxicity was related to dose. From the Second National Wilms' Tumor Study, Thomas *et al*. (14) reported that 16 out of 303 patients developed liver toxicity after surgery, abdominal radiotherapy, and chemotherapy. The radiation dose was administered age-dependently; 166 received more than 30 Gy, while 134 patients received 15-30 Gy. Thirteen (8.6%) out of 151 patients receiving right-flank or whole abdominal radiotherapy exhibited toxicity. By contrast, only three (2%) out of 152 patients receiving left-flank radiotherapy showed hepatic toxicity.

Taken together, a dose effect and volume effect has been confirmed by several reports. The differences were not statistically significant in all analyses, sometimes due to quite small patient numbers. Radiation with doses <20 Gy to major parts of the liver or higher doses to smaller parts (*e.g.* the left lobe of the liver) seems to be safe in children and adolescents. Detailed dose–volume tolerance information is needed but not yet available.

Kidneys. While radiation nephropathy is a well-recognized potential consequence of irradiation in adults (15), less is known about the radiation sensitivity of the kidneys in children. Consequently, information obtained from adults is often extrapolated to pediatric patients. An overview for adults is given by Cassady (16). Several single reports describe late effects in the kidneys after treatment for Wilms' tumor, without detailed information regarding radiotherapy parameters (16-20). Children with Wilms' tumor are at risk for impaired renal function from therapy due to the use of potentially nephrotoxic chemotherapeutic agents, surgical removal of renal tissue, and radiotherapy. An analysis for the distinction between the impacts of the different treatment strategies is sophisticated and has not been performed yet.

In a report from the National Wilms' Tumor Study Group with a database of 5,823 children, Ritchey *et al*. (17) reported 55 patients with renal failure (39 patients with bilateral tumors). Twenty-four of these patients received radiation therapy to the renal parenchyma, nine of whom subsequently underwent bilateral nephrectomy; the other 15 children received radiation doses of 12-20 Gy to the remaining renal parenchyma. Six of these 15 patients developed radiation nephritis. A correlation of functional impairment with the renal radiation dose was reported by Mitus *et al*. (18) in a report of 100 children treated for Wilms' tumor. The incidence of impaired creatinine clearance was significantly higher for children receiving >12 Gy to the remaining kidney, and all cases of overt renal failure occurred in patients who had received >23 Gy.

Pötter *et al*. (19) observed no clinical renal dysfunction in their study on 17 children suffering from Hodgkin's disease who had been treated with radiotherapy (paraaortic field and the splenic pedicle, 18-40 Gy), but subclinical impairment (tested by renal clearance with ^{99m}Tc MAG3) was observed in patients who had received 20 Gy to both kidneys in combination with a dose above 30 Gy in the upper half of one kidney. A clear-cut regional reduction in uptake was observed after radiation doses above 45 Gy to the upper pole

of the left kidney, whereas only a slight regional reduction occurred after doses of 30-40 Gy and none after radiation doses below 30 Gy.

Smith *et al*. (20) evaluated the long-term renal function in 81 children with synchronous bilateral nephroblastoma patients who underwent surgery, received chemotherapy (actinomycin D, vincristine) and were irradiated with 10-20 Gy. Renal function was assessed by measuring blood urea nitrogen and serum creatinine. Twenty-eight children (34.6%) had elevated urea nitrogen and/or creatinine levels, and 18 had moderate and 10 had marked renal insufficiency. In a comparison of the radiation doses of patients with elevated blood values to those with normal values, no dose–response relationship could be established. The renal complication rate was moderate, and other factors including surgery, extent and nature of chemotherapy, and recurrent tumor also had to be taken into account.

The effect of low–dose irradiation (11-13 Gy) on subsequent compensatory renal enlargement in a group of 11 children operated upon with unilateral nephrectomy for Wilms' tumor was reported by Cassady *et al*. (21). The comparison groups were 13 children whose remaining kidney received either no direct irradiation or irradiation to only the upper portion of the kidney (6 children). A study of 19 patients with Wilms' tumor found no significant difference in glomerular filtration rate between patients who received radiotherapy (median 3.3 Gy to the remaining kidney) and those who did not (22).

Taken together, radiation induced kidney function impairment in children seems to be rare. Late renal sequelae may occur in patients who undergo nephrectomy and radiation to the remaining kidney or who receive higher doses to both kidneys.

Gastrointestinal tract. Late gastrointestinal complications of radiation therapy have been recognized but not extensively studied in children. Coia *et al*. (23) describe the late effects of radiation on three gastrointestinal sites in adults. The etiology, pathogenesis, and management of radiation enteritis are discussed by Sher and Bauer (24). Severe long–term toxicity seems to be rare. Manifestations of gastrointestinal toxicity include dysphagia, vomiting, abdominal pain, diarrhea, bleeding and anorexia. Intolerance to fat, milk, gluten, and fiber-containing food may be observed in abdominally irradiated children and cause growth and weight deficits (25). The United Kingdom Children's Cancer Study Group (UKCCSG) (26) characterized the early and late toxicity of 138 patients who had received abdominal radiotherapy within multimodal therapy of Wilms' tumor. In this group, four patients experienced late gastrointestinal effects and required laparotomy for adhesions, 7 to 11 years after diagnosis. None of them had had a second-look laparotomy after chemotherapy. Three had received flank radiotherapy and one had had whole abdominal radiotherapy with doses of 20 or 30 Gy. Paulino *et al*. (27) reported 6 patients with small bowel obstruction in a cohort of 42 children with nephroblastoma. This corresponded to an actuarial incidence of bowel obstruction of 9.5%, 13.0% and 17.0% at 5, 10, and 15 years, respectively. All children underwent abdominal surgery prior to radiotherapy. In two cases, small bowel obstruction was primarily attributed to the initial surgery. The other four patients had small bowel obstruction at 9 to 158 months after nephrectomy and postoperative radiotherapy. Hemi-abdominal or whole-abdomen radiotherapy was performed with doses <12 Gy in two cases; the other four patients received doses up to 40 Gy. The most common cause of an obstruction was a bowel adhesion; the use of radiotherapy was not found to increase the incidence of small bowel obstruction.

Severe gut toxicity with bowel obstructions leading to death was reported in several French Ewing's tumor patients (28). Twenty-eight patients received radiotherapy to the digestive tract after busulfan/melphalan high–dose chemotherapy. After a median follow-up of 31 months, four lethal digestive toxicities were observed. All patients with fatal toxicities had been irradiated with doses exceeding 50 Gy in maximum to large bowel volumes. In an analysis of a similar patient collective in Germany, after a median follow-up of 21 months no severe bowel toxicity was found (29) in 24 patients who had been irradiated with a median maximum dose to the bowel of 45 Gy (24-58 Gy) after busulfan/melphalan high–dose chemotherapy. However, patients had been irradiated with lower doses and smaller volumes in comparison to those treated in France. This may be the reason for the absence of severe problems in Germany. This led to the conclusion that if axial site irradiation is part of the local treatment modality in patients with axial tumor sites, busulfan/melphalan high–dose therapy should be avoided unless irradiation of organs at risk can be avoided using new technical radiotherapy approaches such as proton therapy or intensity modulated radiotherapy.

The limitation of all available studies on late sequelae to the bowel is that they all include abdominal surgery as a further risk factor for the development of late gastrointestinal effects. Ritchey *et al*. (30) reported that after nephrectomy for Wilms' tumor 6.9% of children (131/1910) developed small bowel obstruction. There were several factors that influenced this rate (*e.g*. higher local tumor stage), but the incidence of postoperative small bowel obstruction was not higher in children who received postoperative radiation therapy in comparison to those who had not. Radiation therapy was randomized for stage II (0 *vs*. 20 Gy) and stage III (10 *vs*. 20 Gy) patients with favorable histology. Within the first group, 6.1% of patients (9/139) without radiation and 9.2% of patients (12/112) with radiation developed small bowel obstruction (not significantly different). Within the second group 8.3% of patients (11/122) with radiotherapy of 10 Gy and 11.3% of patients (16/127) with radiotherapy of

20 Gy developed small bowel obstruction (not significantly different). There were only three children in whom the surgeon described operative findings of radiation enteritis.

In conclusion, there are no detailed data regarding the rate of late gastrointestinal complications after abdominal radiotherapy in children. Several reports describe small bowel obstruction as a sequel of surgery, but radiotherapy seems to be less important.

Other side effects. There are further potential side-effects after abdominal irradiation in children. Only a short overview is given here because there are already other reviews on these impairments (8, 9, 31). Impairment of skeletal growth, including scoliosis, and soft-tissue hypoplasia are common and important late side-effects in children. In brief, an incomplete growth arrest of enchondral ossification is observed at doses of 10-20 Gy and permanent arrest at 20-30 Gy (32). Secondary malignancy is also of major concern in pediatric radiation oncology. The cumulative risk of second malignant neoplasms in childhood cancer survivors at 20 years post treatment ranges from 3% to 10% and is 3 to 20 times greater than that expected in the general population (31). In the cohort of the American Childhood Cancer Survivor Study, multivariate analyses adjusted for radiation exposures found that second malignant neoplasms were independently associated with female sex, younger age at diagnosis, childhood diagnosis of Hodgkin's lymphoma, or soft tissue sarcoma and exposure to alkylating agents (31).

Conclusion

Several reports with retrospective evaluations of late sequelae after radiotherapy in childhood and adolescence have been published. However, there is still a lack of information regarding the dose–volume effect relationships. Many of the published reports are limited due to the small patient collectives. It is often difficult or impossible to determine to what degree the late sequelae were due specifically to radiotherapy rather than to surgery or chemotherapy. Other limitations in most of these analyses are inhomogeneous dose distributions, high single doses, insufficient information on organ dose levels, and sometimes older radiation techniques that cannot be compared to modern radiotherapy. Comparisons to current multimodal therapy approaches should therefore be made with caution.

The characterization of late effects after cancer therapy in childhood is of rising interest (6, 33). In the United States of America, the Childhood Cancer Survivor Study has been established to retrospectively characterize the health status of 5-year survivors of childhood cancer (2, 31, 34). In these studies, more than 12,000 patients were evaluated by questionnaire regarding their health status. For radiotherapy, this study cannot give detailed information as to late side-effects due to there being few data on radiation doses and organ dose levels. The study database consists of basic information on the date of radiotherapy, radiation site (*e.g.* thorax, head, and abdomen), tumor doses, and radiotherapy treatment unit (*e.g.* linear accelerator). However, this database does not record the doses to organs at risk, so these may only be calculated retrospectively (34). To counter the described limitations of retrospective evaluation of radiotherapy-associated late sequelae, the German Group of Pediatric Radiation Oncology (APRO) established the Registry for the Evaluation of Late Side Effects after Radiation in Childhood and Adolescence (RiSK). The aim of this prospective, multicenter register is to evaluate the dose-effect relationships of organ dose levels and late side-effects. The feasibility of RiSK has already been shown (35), and initial results were recently published (33). Further collection of treatment data and a longer follow-up period of toxicity documentation are needed though for detailed analyses of the organ dose-effect relationship. Until then, treatment decisions must be based on the available retrospective data.

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