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Review Article

Review – Late toxicity of abdominal and pelvic radiotherapy for childhood cancer

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ABSTRACT

As survival improves in childhood cancer, prevention of late treatment-related toxicity in survivors becomes increasingly relevant. Radiotherapy is an important contributor to late toxicity. Therefore, minimizing radiation exposure to normal tissues is an important step towards improving the long-term therapeutic window of childhood cancer treatment. Since children are growing and developing, they are particularly vulnerable to radiation exposure. This makes the 'as low as reasonably achievable (ALARA)' principle even more important. In order to guide and achieve clinically meaningful dose reductions through advanced and emerging radiation techniques, it is important to investigate age-dependent relationships between radiation exposure to healthy tissues and late radiation-induced toxicity. In this review, we provide an overview of literature on the association between radiotherapy dose and late toxicity after abdominal and pelvic irradiation in childhood cancer. With this information, we aim to aid in decision-making regarding radiotherapy for childhood cancer.

Treatment for childhood cancer has evolved considerably over the last decades, resulting in improved survival. Nowadays, 5-year cancer survival rates in children exceed 80% [1].

Current childhood cancer survivors (CCS) have an increased risk of late morbidity and mortality, not only related to the index cancer itself, but also from its treatment. The 20-year cumulative incidence of grade 3–5 late toxicities in survivors treated between 1990 and 1999 was over 25%, compared to less than 5% in their siblings [2].

Radiotherapy (RT) is an important factor contributing to late toxicity. Its late effects include a wide spectrum of health problems. Examples include the development of second malignant neoplasms (SMNs), renal insufficiency and gonadal failure [3–4]. In a substantial long-term cohort study, CCS who received RT had relative risks compared to siblings of 3.4 for developing grade 1–4 chronic conditions, 7.9 for developing grade 3–4 chronic conditions, and 5.2 for developing multiple chronic conditions. Relative risks were highest after RT to the chest, abdomen or pelvis [5]. In another long-term follow-up cohort, abdominopelvic radiotherapy was associated with an increased risk of hospitalization, among other causes due to endocrine, nutritional and metabolic diseases (relative hospitalization rate (RHR) 2.5), as well as subsequent neoplasms (RHR 1.7) [6].

In paediatric literature, associations between RT and late toxicity have historically been based on prescribed dose to the target volume. However, for adequate quantification of toxicity, normal tissue complication probability (NTCP) data is required, describing the relation between radiation dose to a tissue in relation to the endpoint (toxicity) of interest. For such models, information on the actual dose to healthy tissues is required, but often unavailable in long-term cohorts of survivors treated with older RT techniques.

Abbreviations: ALT, Alanine aminotransferase; CCS, Childhood cancer survivors; CCSS, Childhood cancer survivor study; CI, Confidence interval; DM, Diabetes mellitus; eGFR, Estimated glomerular filtration rate; FSH, Follicle stimulating hormone; GFR, Glomerular filtration rate; GGT, Gamma-glutamyl transferase; IGHG, International Guideline Harmonization Group; LCD, Leydig cell dysfunction; LCF, Leydig cell failure; LH, Luteinising hormone; NTCP, Normal tissue complication probability; PBT, Proton beam therapy; PENTEC, paediatric normal tissue effects in the clinic; QUANTEC, Quantitative analysis of normal tissue effects in the clinic; RR, Relative risk; RT, Radiotherapy; SMN, Second malignant neoplasm; TBI, Total body irradiation.

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Examples of methods for tissue dose estimation include retrospective dose reconstruction using mathematical phantoms, radiobiological dose metrics (i.e., estimation of biological effectiveness), and prospective registration of RT planning system data. Toxicity may be prevented or reduced by adapting treatment plans guided by the dose parameters that are most relevant for the development of late radiation-induced side effects or using more advanced techniques like proton beam therapy (PBT) in order to reduce dose to the organ at risk (primary prevention).

In the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) review, RT dose, volume and outcome data were summarized to provide tolerance guidelines for the clinic [7]. Unfortunately, these guidelines are mostly based on data from adult patients, with limited generalizability to the more complex and heterogeneous paediatric population. More recently, the Paediatric Normal Tissue Effects in the Clinic (PENTEC) collaboration has been launched, which aims to perform a systematic review of dose/volume/outcome data in children and provide dose/volume tolerance guidelines specifically for the paediatric population [8].

In this review, we provide an overview of current literature about the association between RT to the abdomen or pelvis for childhood cancer and late toxicity excluding secondary cancers and bone growing defects. A special focus was placed on studies investigating dose–effect relationships and studies developing normal tissue complication probability (NTCP) models of late toxicity (i.e., prediction models describing the relationship between radiation dose and other parameters and the risk on a given adverse effect) investigating RT dose to the abdomen and/or pelvis as a possible predictor.

Materials and methods

Selection criteria

All study designs investigating the association between RT for childhood cancer and late adverse effects to organs in the abdomen and pelvis were eligible, except for case reports, case series (description of non-consecutive cases), and studies including fewer than 20 patients. The studies had to include childhood cancer survivors diagnosed between the ages of 0 and 18 years, who were at least one year after completion of their cancer treatment. Selected papers needed to include treatment with RT involving the abdomen or pelvis, including total body irradiation (TBI). Combinations with other treatment modalities, such as surgery and chemotherapy, were allowed.

The type of outcome measure included late adverse effects that could be attributed to RT (present at least one year after RT) for each organ in the abdomen and pelvis. Late toxicities related to irradiation of the pancreas, liver, kidneys, spleen, intestines, bladder, testes, ovaries and vagina were included. Second malignant neoplasms were not included as an outcome in this study, since the broad spectrum of secondary tumours potentially arising from radiotherapy to the abdomen and pelvis would warrant one or more separate literature studies.

Search methods

A literature search was performed in the Cochrane Library and MEDLINE (PubMed). The search terms used are summarized in Tables S1-2. The flowchart of literature search steps in the Cochrane library, International Guideline Harmonization Group (IGHG) guidelines and PubMed (MEDLINE) is shown in Fig. 1. Only articles written in English were reviewed.

If a Cochrane review existed for a relevant outcome, the results from this Cochrane review were reported and a MEDLINE search was performed only for studies published after its scope. Studies included in the Cochrane reviews are not cited separately; we refer to the relevant Cochrane publication.

The reference lists of all relevant articles and reviews were screened for additional references which were not found in the initial search.

Data collection and analysis

After performing the search strategy described above, one review author selected the studies meeting the inclusion criteria. In case of doubt during the selection process, a second author was asked to review the abstracts. For all studies possibly meeting the inclusion criteria based on title and/or abstract, the full text was reviewed. Special emphasis was placed on finding articles reporting on dose–effect relations of RT with late toxicity.

Studies meeting the inclusion criteria were categorised according to the evidence level regarding the relation between radiation dose to the organ and the toxicity of interest. These evidence levels, as formulated by the authors of this manuscript, are summarized in Table 1. Category A is the highest; studies with this level describe clear dose effect relations. Category D is the lowest and is reserved for studies not describing a clear association between radiotherapy and the outcome of interest.

If studies with different evidence categories were found for the same outcome, only the studies with the highest evidence category for that outcome were described in more detail (e.g., all category A studies if available). Results for each study were reported based on the information available in the articles and appendices. Study characteristics were described for each study, including the number of participants, time period of treatment and RT dose used.

Results

Results of literature screening in CENTRAL, IGHG guidelines and MEDLINE are shown separately and per organ in Table S3. Characteristics of the studies included in this review are summarized in Tables S4-5 for toxicities of abdominal organs, and in Tables S6-7 for toxicities of pelvic organs.

Late effects of RT to the abdomen

Pancreas

Diabetes mellitus (DM) is associated with an increased risk of cardiovascular disease and subsequent mortality [9–10]. CCS are at increased risk of developing DM. Exposure to abdominal irradiation or TBI adds to this risk [11]. QUANTEC does not specify constraints for dose to the pancreas [7].

Out of 12 papers meeting inclusion criteria [12–23], two reported on a category B dose–effect relation (Table 1) [15,18].

In both category B studies, RT dose delivered specifically to the pancreas tail ($\geq$10 Gy) was associated with the risk of developing DM [15,18]. This dose–effect relation was most pronounced in young children (<2–10 years) and declined with higher age at treatment [15,18]. No dose–response relation was found in children $\geq$15 years at diagnosis [18]. Chemotherapy use was not associated with risk of developing DM and did not influence the dose–response relations [15,18]. One study analyzed the effect of the number of fractions, which was not statistically significant [15].

Based on this information, in contrast to the QUANTEC recommendations, the pancreas tail should be delineated as an organ at risk for children $\leq$ 10 years of age [15,18]. The dose delivered to the pancreas tail should be $\leq$ 10 Gy. Since the ERR per Gy increases with lower age at diagnosis, constraints should be even stricter in children who are younger (especially those <2 years) at time of diagnosis.

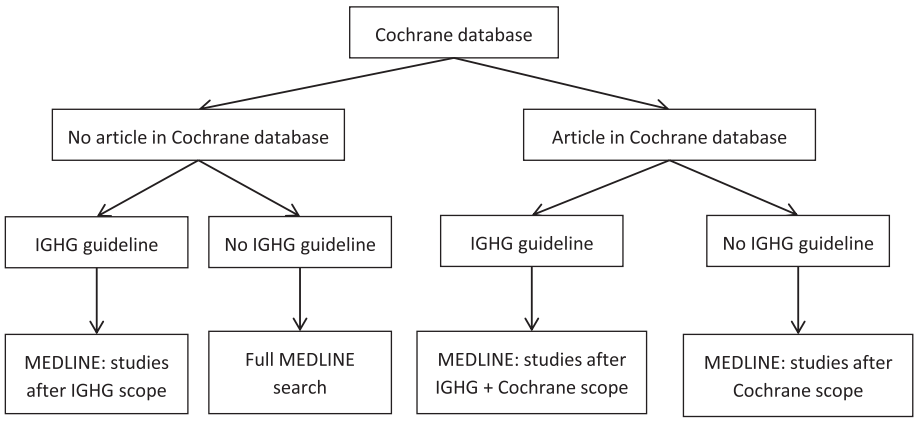

Fig. 1. Flowchart of literature search steps. IGHG International Guideline Harmonization Group; MEDLINE Medical Literature Analysis and Retrieval System Online.

Table 1
Explanation of Evidence Categories.

Category	Explanation
A	RT as significant predictor in NTCP model predicting absolute risk of an adverse effect
B	RT dose significantly associated with occurrence of adverse effect, but no prediction model for absolute risk of the outcome exists that includes RT dose
C	RT associated with outcome, but no dose–effect relation reported in literature
D	No clear association described between RT and outcome

NTCP normal tissue complication probability; RT radiotherapy.

Liver

Late radiation-induced hepatobiliary complications, such as hepatic fibrosis, cirrhosis, or cholelithiasis, are uncommon in long-term CCS, but have been described in patients receiving higher doses [24]. QUANTEC advises mean liver doses of <13–20 Gy, depending on the primary cancer and fractionation, or ≤15 Gy to ≥700 mL of normal liver [25].

A Cochrane review (updated 2019) [26] found that, based on current evidence, radiotherapy involving the liver is suggested to be a risk factor for cellular liver injury (*i.e.*, elevated alanine aminotransferase (ALT)) [27,28] and biliary tract injury (category C) [27]. Furthermore, the percentage of the liver volume irradiated (*i.e.*, the V10, V15 and V20) was suggested to be related to the risk of cellular liver injury (category B, see Table 1), independently of the effects of busulfan and thioguanine use on this outcome. The effect of age at diagnosis on this outcome was not reported [28]. The clinical relevance of these laboratory abnormalities remains uncertain [26]. One IGHG guideline on the topic has been published [29], referencing the same study [28]. A MEDLINE search for articles published after the scope of the Cochrane review (January 2018) did not yield additional relevant articles.

The limited available data summarized here are insufficient to recommend different dose constraints from those of QUANTEC when treating children with radiotherapy [25].

Kidneys

Nephrotoxicity after RT may become clinically apparent as hypertension, a decline in GFR and proteinuria [30]. QUANTEC advises bilateral mean kidney doses <10 Gy (TBI) or <18 Gy (non-TBI) for a <5% toxicity risk. If one kidney receives >18 Gy, <30% of the remaining kidney's volume may receive >6 Gy. Age <5 years has been associated with a higher risk of renal dysfunction after RT [31].

One Cochrane review was found on the topic (updated in 2019) [32]. It identified several studies reporting on associations between RT and kidney-related outcomes such as reduced eGFR [33–37], proteinuria [33,34,38], and elevated blood pressure [12,34,39–41]. Most studies did not find significant associations of RT with renal outcomes (category D, see Table 1).

Seven additional MEDLINE articles published after the scope of the Cochrane review (*i.e.*, March 2017) were found [42–48]. Four articles described category B dose–effect relations (Table 1) [43,46–48].

The first study found significantly lower eGFR after abdominal RT for Wilms' tumour. In addition, cystatin-based eGFR showed a significant moderate correlation with prescribed irradiation dose, with a trend towards lower eGFR after prescribed doses ≥25 Gy. No association with nephrotoxic chemotherapy was found in this study. The effect of age at diagnosis was not reported [43]. The second study, based on the Childhood Cancer Survivor Study (CCSS) cohort, found in multivariable analysis that TBI (HR 6.9) and non-TBI estimated mean kidney dose >15 Gy (>15–20 Gy: HR 3.6; >20 Gy: HR 4.6) were both associated with an increased risk of requiring kidney transplantation later in life. Ifosfamide use and nephrectomy, but not methotrexate use or age at primary cancer diagnosis, were also independently associated with this outcome [46]. In the third study, based on the SJLIFE cohort, the volumes of kidney receiving ≥5 Gy and ≥10 Gy were associated with an increased risk of stages 3–5 chronic kidney disease in multivariable analysis. Ifosfamide, cis-Platinum and Carboplatinum dose (mg per m^2), as well as calcineurin inhibitere use, were independently associated with increased risk. The effect of age at diagnosis was not reported [48]. Lastly, the fourth study, based on the CCSS cohort, described an increased risk of late-onset kidney failure after kidney doses ≥15 Gy in multivariable analysis. Anthracycline and ifosfamide dose (g/m^2) were also associated with increased risk, while age at diagnosis did not have a significant effect [47].

Based on the presented data, there is no clear indication to deviate from the current QUANTEC recommendations in radiotherapy for children, nor to make a distinction between different age groups.

Spleen

Asplenia, whether anatomic due to splenectomy or functional, e.g., due to RT, is associated with an increased risk of severe infection by encapsulated bacteria such as *streptococcus pneumoniae* [49]. No tolerance dose has been specified by QUANTEC. Previously, risk of impaired splenic function was mainly expected to occur after treatment RT doses ≥40 Gy [50].

Out of 2 articles meeting inclusion criteria one was assigned as category B (Table 1) [51].

In a large cohort study, the risk of late infection-related mortality increased with radiation dose to the spleen (reconstructed average dose to the left upper quadrant of the abdomen was used as a surrogate) from a 2-fold increase in doses <10 Gy (P = 0.08) to a 5.5-fold increase in doses ≥10 Gy (P = 0.001) in multivariable analysis (translating to a cumulative incidence at 35 years of 0.4% (95% CI, 0.2–0.6%), 1.1% (95% CI, 0.2–2%), and 1.3% (95% CVI 0.2–2.4%) after 0.1–9.9 Gy, 10.0–19.9 Gy, and ≥20 Gy to the spleen, respectively). A cyclophosphamide equivalent dose of chemotherapy ≥8000 mg/m^2 was independently associated with late infection-related mortality. Age at diagnosis did not affect the outcome [51].

Based on the aforementioned study, in contrast to the current QUANTEC recommendations in adults, we would recommend including the spleen as an organ at risk in children and striving for a mean dose to the spleen <10 Gy in all age groups to minimize the risk of late infection-related mortality. Since this is a single study, independent confirmation of the findings is warranted.

Late effects of RT to the pelvis

Intestines

Irradiation to the intestines can lead to several types of toxicity, such as enteritis, adhesions and fibrosis. The QUANTEC guidelines recommend keeping the volume of delineated bowel loops receiving ≥15 Gy under 120 cc, or keeping the volume of peritoneal cavity receiving ≥45 Gy under 195 cc. Both surgery and chemotherapy increase the risk of radiation induced bowel toxicity [52].

After literature screening 2 category B articles were deemed relevant for this review (Table 1) [53,54].

In multivariable analysis of a large study of CCS, increasing abdominopelvic prescribed dose (≥20 Gy) in patients with abdominopelvic tumours was associated with an increased risk of intestinal obstruction requiring surgery. Chemotherapy use and age at diagnosis did not show an independent association with this outcome [53]. In a more recent study from the same group, pelvic RT (prescribed dose ≥30 Gy) was associated with an increased risk of late anorectal disease (combined outcome including fistula and stricture), translating to a cumulative incidence 40 years after diagnosis of 2.7% (95% CI 2.4–3.1%), 3.9% (2.5–5.2%), and 9.7% (4.8–14.7%), in all survivors and dose with pelvic prescribed dose 30–49.9 and ≥50 Gy, respectively. Platinum dose was not associated with this outcome. The effect of age at diagnosis was not reported [54].

Since the aforementioned studies only report prescribed dose to abdomen and/or pelvis, these data are insufficient to deviate from current OAR constraints as advised by QUANTEC or to recommend different constraints based on age group.

Bladder

Haemorrhagic cystitis, fibrosis or hypoplasia are the most frequently reported radiation-induced bladder complications. Symptoms of haemorrhagic cystitis include urgency, frequency, dysuria, stranguria and haematuria [55]. Treatment may involve antispasmodic drugs, saline bladder irrigation, or in severe cases cystoscopy with clot evacuation or even cystectomy [56]. According to the QUANTEC guidelines, no reliable literature-based constraints are currently available [57].

Four studies provided useful information on the association between pelvic RT and haemorrhagic cystitis [56,58–60].

In two studies, pelvic RT (for various malignancies, presumably excluding TBI, dose not reported) was associated with a higher incidence of haemorrhagic cystitis, occurring in 30–60% of irradiated patients versus 1–6% of non-irradiated patients (category C, see Table 1) [58,60]. In another study, pelvic RT (for various malignancies, dose not reported) was associated with more severe (grade III or IV) haemorrhagic cystitis and more frequent need of invasive management such as continuous bladder irrigation or operative intervention (category C) [56]. In contrast, one older study (n = 977), including patients undergoing bone marrow transplantation for various diseases (presumably after TBI), did not find an association between use of RT and incidence of haemorrhagic cystitis (category D, see Table 1) [59].

The aforementioned data, like the adult data available to QUANTEC, are insufficient to recommend specific dose constraints to the bladder for radiotherapy in children.

Female gonads (ovaries and uterus)

Ovarian failure is a common late effect of RT, occurring in 30–40% of patients receiving RT or chemoradiotherapy for pelvic tumours. Ovarian failure may result in a myriad of health problems including premature menopause and infertility [61]. QUANTEC does not specify a maximum dose for the ovaries [7].

Like the ovaries, the uterus serves an important function in female fertility. Radiation toxicity to the uterus may therefore have profound consequences for female childhood cancer survivors. QUANTEC does not mention specific dose constraints for the ovaries or uterus [7].

One article with category A evidence [62], and nine articles with category B evidence were found on ovarian failure (Table 1) [11,63–70]. The former article will be described in more detail [62]. Also, two IGHG guidelines [71,72] and 13 category B MEDLINE articles [69–70,73–83] on different adverse outcomes after ovarian and uterine irradiation met inclusion criteria. Lastly, a relevant review on the topic will be discussed [84].

In the aforementioned category A study, a prediction model was developed combining the cohorts from the CCSS (n = 5886) and the St. Jude Lifetime Cohort (SJLIFE) study (n = 875). A linear dose–response relationship was found between the minimum ovarian dose (i.e., lowest of the average doses to the left and right ovaries) and the risk of acute ovarian failure. In a prescribed dose model, a linear dose–response relation was found between the prescribed abdominal and pelvic dose, and the risk of acute ovarian failure [62]. An online calculator has been published on the CCSS website (https://ccss.stjude.org/tools-documents/calculators-other-tools/ccss-ovarian-risk-calculator.html) to predict absolute risk of acute ovarian failure based on ovarian or prescribed RT dose, also taking into account other predictors, such as the cyclophosphamide equivalent dose (mg/m^2 of chemotherapy (increasing risk after higher dose) and age at cancer diagnosis (increasing risk with higher age; *i.e.*, lower risk at prepubertal age) [62].

An IGHG guideline on premature ovarian insufficiency reports on four studies describing dose–response relations with premature menopause [65,85–87]. The guideline authors concluded that radiotherapy to the ovaries was associated with an increased risk of premature menopause, especially for women who were treated with higher doses, although definition of a clear threshold for a safe RT dose could not be given [71]. In other studies found through MEDLINE, doses >0–5 Gy absorbed by the ovaries have been associated with premature menopause. Higher chemotherapy dose [74,76,82], and higher age at treatment were also associated with premature menopause in all studies [74,76,82]. A review concludes that high-quality evidence exists for the relation between ovarian dose and the risk of premature ovarian insufficiency, and moderate-quality evidence for further increase in risk when ovarian radiotherapy is combined with alkylating agents [84].

Dose-effect relationships (category B) have also been described between lower abdominal/pelvic RT and hormonal markers of low ovarian reserve (prescribed dose >0 Gy). In multivariable analysis, procarbazine dose was also an independent risk factor. Age at diagnosis was not included in the analysis [69]. Radiotherapy doses

≥4–5 Gy received by ovaries or uterus were associated with subfertility [70,73,77–79]. In addition, higher chemotherapy dose increased this risk [70,77,79], with combined chemoradiotherapy as an independent risk factor [78]. In some studies no effect of age was identified [70,78], while in others a younger age at diagnosis (<10 years) was associated with a lower risk of subfertility [77,79].

The aforementioned review concludes that moderate quality evidence exists for the relation between ovarian RT dose and the likelihood of pregnancy and livebirths, as well as low-quality evidence for decreasing likelihood of this outcome after increasing doses of cyclophosphamide, busulfan and lomustine [84].

An IGHG guideline was published on obstetric outcomes in CCS [72]. It concludes that very low level evidence exists for dose–response relations of radiotherapy with gestational hypertension and malposition [88], low level evidence for miscarriage [80,89], premature birth (>5–15 Gy received by ovary and uterus) [81,88], and small size/stature for gestational age [81,89], and moderate level evidence for low birthweight (>2.5/25 Gy) [78,81,89]. Several MEDLINE articles also described dose–effect relations with obstetric outcomes (category B). Doses of >1–10 Gy to these organs were associated with stillbirth and neonatal death [80,83]. Chemotherapy with alkylating drugs was not associated with this outcome [83]. Age at diagnosis did not affect the risk in one study [80], while irradiation before menarche was a risk factor for stillbirth and neonatal death in the other [83]. Doses of >5 Gy to the uterus and >0.5–2.5 Gy to the ovaries, as well as treatment with higher doses of alkylating chemotherapy, have been associated with preterm delivery, low birth weight and small stature of children born form female CCS [73,81]. These risks increased in patients diagnosed before 10 years [73]. Radiation doses received by the uterus as low as ≥2.5 Gy during childhood were associated with miscarriage in one study, especially in women with a smoking history of >5 pack years ($P_{\text{interaction}} = 0.01$). The study did not report on the effects of chemotherapy and age at diagnosis on this outcome [75].

Based on the collection of data summarized above, every achievable dose avoidance to the gonads is warranted in radiotherapy for childhood cancer. If total avoidance is impossible, at most <5 Gy to ovaries or uterus should be strived for. The risk of late complications is even higher when alkylating chemotherapy is used. While the risk of premature menopause and subfertility tends to be lower in patients younger than 10 years, the risk of later pregnancy and obstetric complications tends to increase in younger patients. Therefore, we recommend the same constraints for all female pediatric patients.

Vaginal toxicity and sexual functioning

Vaginal RT has been associated with decreased vaginal length as well as increased dyspareunia, resulting in pain and decreased sexual satisfaction [90]. QUANTEC does not report constraints for vaginal RT dose [7].

The literature review resulted in one category C article meeting inclusion criteria for the present review (Table 1) [91].

In the aforementioned study, young adult female CCS who had received TBI (dose not reported) before hematopoietic stem cell transplantation during childhood, reported lower Female Sexual Function Index score, indicating issues in sexual functioning, and showed a trend towards shorter vaginal length compared to survivors in the chemotherapy and RT (chest or abdominopelvic, dose not reported) group [91].

The aforementioned study provides insufficient information to recommend specific dose constraints for the vaginal wall.

Testicular irradiation: fertility

The testes consist of two main cell types, including the spermatogonia and Leydig cells. The spermatogonia, which are responsible for spermatogenesis, are the most sensitive to RT. Though QUANTEC does not report specific constraints [7], permanent impairment of spermatogenesis has been reported even after a radiation dose of <2–3 Gy [92].

One IGHG guideline [92] and three MEDLINE studies reporting on a dose–effect relationship (category B, see Table 1) between RT and either fertility [93,94], or azoospermia [95], were found in the literature review. In addition, a relevant review on the topic will be discussed [96].

The IGHG guideline describes no studies on dose–effect relations for impaired spermatogenesis [92]. In the first MEDLINE study, testicular radiation dose ≥4 Gy was associated with an increased risk of infertility compared to lower doses or no RT. Alkylating agent dose and bleomycin exposure were also independent risk factors. Age at diagnosis was not included in multivariable analysis [93]. In the second study, testicular radiation dose ≥7.5 Gy was associated with a lower probability of siring a pregnancy ≥5 years after diagnosis, while no effect was found for lower doses. In multivariable cox regression, older children (15–20 years) were more at risk for radiation-induced infertility than children irradiated at a young age (0–4 years), as were patients receiving higher cumulative alkylating agent dose or treatment with cyclophosphamide or procarbazine [94]. The third study reported that participants with azoospermia had received higher gonadal RT doses (median 0.3 Gy), and were more frequently treated with alkylating agents, compared to patients who retained sperm production after gonadal irradiation (median 0.03 Gy). The influence of age at diagnosis was not reported [95]. A review on the topic describes that high-quality evidence exists for an increased risk of impaired spermatogenesis and testosterone deficiency after testicular RT as well as after higher doses of alkylating agents. The authors concluded that conflicting evidence existed regarding the role of age at diagnosis in the risk of impaired spermatogenesis, with one study providing low-quality evidence for a higher risk with older age at diagnosis, while two other studies did not reproduce this association [96].

Based on the aforementioned studies, dose on the male gonads in childhood radiotherapy should be kept as low as possible, preferably 0 Gy but at most <7.5 Gy. While evidence is inconclusive about the influence of age, the risk seems to be highest for teenagers.

Testicular failure

Leydig cells, responsible for testosterone production, are less radiosensitive than spermatogonia and can tolerate doses up to 12 Gy without increased risk of testosterone deficiency [92].

The literature search (Table S3) resulted in one IGHG guideline [92], as well as two MEDLINE articles of category B evidence (Table 1) [11,97].

The IGHG guideline describes no studies on dose–effect relations with testosterone deficiency [92]. In a study from the CCSS, testicular irradiation ≥20 Gy or cyclophosphamide equivalent dose ≥20 g/m^2 was associated with an increased prevalence of need for testosterone replacement. The study did not report the relation of age at diagnosis to this outcome [11]. In another large cohort study of CCS (n = 1516), testicular RT at any dose and alkylating agents at cyclophosphamide equivalent doses of ≥4000 mg/m^2 were risk factors for Leydig cell failure (LCF; testosterone <250 ng/l and LH >9.85 IU/l), while doses ≥12 Gy were significantly associated with Leydig cell dysfunction (LCD; testosterone ≥250 ng/l and LH

>9.85 IU/l). Both outcomes occurred more frequently and earlier in higher testicular dose categories, with 95% of participants receiving testicular doses ≥20 Gy reporting either LCD or LCF. Age at diagnosis was not included in the study [97].

Based on the data presented above, the recommendations mentioned under "testicular irradiation: fertility" (*i.e.*, preferably 0 Gy, but at most <7.5 Gy average dose), should be sufficient to limit the risk of Leydig Cell dysfunction and failure as well.

Discussion

Because of the limited generalizability of the QUANTEC data to the growing and developing paediatric population [7], the paediatric dose/volume guidelines from the PENTEC collaboration are eagerly awaited [8]. Until then, in this review we have aimed to provide a brief but comprehensive overview of literature on dose/volume – effect relations for RT to normal tissue in abdomen and pelvis in children.

Findings and implications

The evidence on late toxicity after abdominal and pelvic RT is summarized in Table 2 and Table 3. Based on the study results presented in this review, RT doses as low as 4 Gy to testes in male and ovaries or uterus in female CCS, especially after onset of puberty, already may have detrimental effects on fertility [69,73–83,85,93,94]. This stresses the importance of reducing RT dose to these organs as much as possible.

Interestingly, several studies describe dose–effect relations between RT to the pancreas tail and the development of DM at considerably lower doses than in adults, especially when RT occurs in the first 2–10 years of life [15,18]. Considering the long-term health consequences of DM, this stresses the importance of sparing the pancreas tail in young children.

The association of even low radiotherapy doses to the spleen with late infection-related mortality [51], in contrast to ≥40 Gy as reported earlier [50], suggests adjustment to follow-up of CCS and to dose constraints for RT planning should be made according to the more recent SIOP -Europe Radiation Oncology Working Group recommendation [98].

Dose-effect relations have also been described for elevated ALT after liver irradiation [28], renal failure after kidney irradiation [43,46,47], as well as anorectal disease and intestinal obstruction after abdominopelvic irradiation [53,54]. The clinical relevance in these cases is less clear, since the clinical consequences of an asymptomatic elevated ALT are unclear [28], and the majority of late toxicity were only significantly elevated after high radiation doses (>15–25 Gy renal dose or ≥20–30 Gy prescribed (abdomino-) pelvic dose) [43,46,47,53,54].

In general, international paediatric treatment protocols give recommendations on tolerance doses to organs at risk. Most of these recommendations are based on the Emami paper [99]. Since radiation oncologists will avoid exceeding these constraints for most treatments, it is not possible to evaluate late toxicity of doses above these constraints.

Strengths and limitations

This study provides a broad overview of known associations between RT dose and late toxicities of abdomen and pelvis in children. Its main strengths are its broad scope and concise reporting, focusing on relevance for clinical practice.

The study also has several limitations. First, in order to provide focus in discussion of a wide range of toxicities, only studies with the strongest evidence category per outcome were discussed, meaning many studies remain unmentioned. This study is therefore intended to give a broad overview of current evidence, rather than as a replacement for systematic reviews performed per toxicity, such as those being performed by the PENTEC collaboration [8]. Second, the review was limited to published English articles that were available full-text. In other words, the study is likely to suffer from reporting bias. Furthermore, the strength of recommendations from this review was dependent on the evidence available per outcome discussed. Information on the number and size of radiotherapy fractions was not provided in most studies, precluding comparisons using equivalent dose in 2 Gy fractions (EQD2). Also, while most studies had information on chemotherapy use and age at diagnosis, this was not always incorporated into multivariable analysis or tested for interactions with radiotherapy dose. Finally, the definition of outcomes across studies is heterogeneous, making interpretation and pooling of results more difficult [100]. Most reported outcomes are based on either prescribed or reconstructed dose and most studies do not provide a detailed description of dose-volume parameters [101].

In order to have better models for predicting radiation induced toxicity in the future, it is important to prospectively and systematically collect toxicity data in combination with 3D-dose-volume parameters to the organs of interest.

Table 2
Conclusions of evidence for late toxicity after abdominal irradiation for childhood cancer.

Toxicities	Category	Recommended dose
Pancreas		≤10 Gy to tail (stricter if <2y)
Diabetes mellitus		
Increased risk after higher dose to pancreas tail vs lower dose (≥10 Gy)	B [20]	
Liver		QUANTEC
Cellular liver injury		
Increased risk after irradiation of a larger liver volume vs lower volume (V10, V15, V20)	B [26,28]	
Biliary tract injury		
Increased risk after irradiation involving the liver vs no radiotherapy	C [26,27]	
Kidneys		QUANTEC
Proteinuria		
Increased risk after radiotherapy potentially involving kidneys	D [32]	
Elevated blood pressure		
Increased risk after radiotherapy potentially involving kidneys	D [32]	
Reduced estimated glomerular filtration rate (eGFR)		
Lower eGFR after higher *prescribed* dose vs lower dose (≥25 Gy)	B [43]	
Lower eGFR after higher irradiated volume (V5, V10)		
End-stage renal disease (e.g., dialysis, transplantation)	B [48]	
Higher risk after higher mean kidney dose vs lower dose (≥15 Gy)	B [46,47]	
Spleen		
Late infection-related mortality		<10 Gy(all ages)
Increased risk after higher dose to spleen vs lower dose (≥10 Gy)	B [51]	

Categories: A dose–response relation quantified in model; B dose–response relation, not directly quantified; C association with radiotherapy, no dose–response relation; D equivocal results (no consistent evidence towards an effect of radiotherapy).

Table 3
Conclusions of evidence for late toxicity after pelvic irradiation for childhood cancer.

Toxicities	Category	Recommended dose	
Intestines		QUANTEC	
Intestinal obstruction requiring surgery			
Increased risk after higher *prescribed* abdominopelvic dose vs lower dose (≥20 Gy)	B [53]		Anorectal disease (fistula, stricture, second malignant neoplasms)
Increased risk after higher *prescribed* pelvic dose vs lower dose (≥30 Gy)	B [54]		
Bladder			Insufficient data
Haemorrhagic cystitis			
Increased risk after pelvic radiotherapy	C [58,60]		
Increased severity after pelvic radiotherapy	C [56]		
Ovaries, uterus		0–<5 Gy to ovaries or uterus(all ages: fertility >10y, obstetric <10y)	
Acute ovarian failure			
Increased risk after a higher ovarian irradiation dose (>0 Gy)	A [62]		
Premature menopause			
Increased risk after higher radiotherapy dose to ovaries (>0–5 Gy)	B [65,74,77,79,85–87]		
Markers of low ovarian reserve			
Increased risk after higher *prescribed* abdominopelvic dose (>0 Gy)	B [69]		
Subfertility			
Increased risk after higher ovarian and/or uterine dose (≥4-5 Gy)	B [70,76,80–82]		
Stillbirth, neonatal death			
Increased risk after higher ovarian and/or uterine dose (>1–10 Gy)	B [75,83]		
Preterm delivery, low birth weight and small stature			
Increased risk after higher ovarian and/or uterine dose (>0.5–25 Gy)	B [73,76,81,88,89]		
Miscarriage			
Increased risk after higher uterine dose (≥2.5 Gy)	B [78,83,89]		
Gestational hypertension, malposition			
Increased risk after higher *prescribed* flank dose (>0 Gy)	B [88]		
Vagina		Insufficient data	
Female sexual function, vaginal length			
Lower sexual function score and shorter vaginal length after total body irradiation	C [91]		
Testes		0–<7.5 Gy(strict ≥10y)	
Sub-/infertility			
Increased risk after higher testicular dose (≥4-7.5 Gy)	B [93,94]		
Azoospermia			
Increased risk after higher testicular dose (median 0.3 Gy)	B [95], D [92]		
Reduced testosterone production			
Increased risk after higher testicular dose (>0–20 Gy)	B [11,97], D [92]		

Categories: A dose–response relation quantified in model; B dose–response relation, not directly quantified; C association with radiotherapy, no dose–response relation; D equivocal results (no consistent evidence towards an effect of radiotherapy).

Conclusions

This review provides an overview of available evidence regarding normal tissue effects of RT in childhood cancer. In particular, we found that significant long-term consequences occur after relatively low irradiation doses to gonads, pancreas tail and spleen compared to adults. This information may help inform clinicians when making decisions on RT planning and long-term follow-up.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.02.029.

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