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Original Article

Late toxicity after upper abdominal radiotherapy in pediatric Wilms tumor and neuroblastoma survivors. A systematic review on behalf of SIOPEN and SIOP-RTSG

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ABSTRACT

Background: Radiotherapy plays a crucial role in the multimodal treatment of Wilms tumor and neuroblastoma subtypes with an increased risk of locoregional failure. Unfortunately, radiotherapy can be associated with late toxicities in survivors. This systematic review provides an overview of the quality of evidence related to late effects following upper abdominal radiotherapy in survivors of Wilms tumor and neuroblastoma.
Method: A systematic search was conducted using the PubMed database to address clinical questions regarding late effects on the liver, pancreas, vessels, kidney(s), musculoskeletal structures, second malignancy induction, spleen, and intestines. The Quality In Prognosis Studies (QUIPS) tool was utilized to assess the risk of bias in individual studies. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool was applied to evaluate the overall quality of evidence concerning late toxicity risks after upper abdominal radiotherapy.

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Results: Out of 3080 records, 55 studies were included. We identified high levels of evidence for the prevalence of metabolic syndrome, diabetes, and functional asplenia as late toxicities following upper abdominal radiotherapy. A moderate level of evidence was found for an increased risk of secondary malignant neoplasms (renal cell carcinomas and colorectal carcinomas) and chronic kidney disease. Very low evidence for prevalence of scoliosis/spinal deformity and aortic growth abnormalities was observed.
Conclusion: This systematic review highlights the different levels of evidence of a spectrum of late toxicities, associated with upper abdominal radiotherapy in survivors from a Wilms tumor and neuroblastoma. Within the multi-disciplinary approach, modern radiotherapy has the potential to limit these late effects.

Introduction

Radiotherapy has an important role in the multimodal treatment of patients with Wilms tumor (WT) and neuroblastoma (NBL) [1]. Improved risk-stratification over the last five decades has resulted in a significant decrease in radiotherapy prescription dose and number of indications for both WT and NBL. Nowadays, flank irradiation is applied in about 20 % of the WT, particularly in stage 2 high-risk tumors with diffuse anaplasia, and stage 3 intermediate/high-risk tumors. Whereas radiotherapy for NBL is still applied in all high-risk NBL protocols and in a highly selected group of incompletely resected medium-risk NBL [2,3]. Recent advancements in radiotherapy techniques have led to increased sparing of surrounding healthy tissues [4,5]. Since 2015 highly conformal target volumes combined with modern radiotherapy techniques have been stepwise introduced for flank irradiation in Wilms tumors to replace the conventional target volumes irradiated via two opposing beams [4,6]. A similar evolution is taking place in the treatment of neuroblastoma [5].

In childhood cancer survivors (CCS) radiotherapy is (strongly) associated with late toxicities that significantly impact quality of life, affecting physical, cognitive, and psychosocial aspects [7]. Moreover, the young age at diagnosis makes survivors of a WT or NBL particularly vulnerable to late effects from radiotherapy [8–10]. While the above mentioned advancements mark important progress, there remains room for further improvement in reducing late effects, for instance by further reducing prescription dose and target volumes, omitting radiotherapy in patients with a favorable molecular profile, and identifying biological predictors of radiotherapy response to guide dose escalation or de-escalation.

Although Pediatric Normal Tissue Effects in the Clinic (PENTEC) recently published organ-specific normal tissue complication probabilities for the spinal column [11], kidney [12], liver [13], and subsequent malignancies [14], a comprehensive overview of evidence on late toxicity associated with upper abdominal radiotherapy in WT and NBL survivors is lacking. By identifying organs at risk and understanding the associated toxicities, this review aims to provide an overview of the quality of evidence related to the late effects following upper abdominal radiotherapy for WT and NBL survivors and may guide potential preventive strategies to further improve long-term outcomes for these survivors.

Methods

Search strategy

Upfront, the core team *(FW, FZ, MH, GJ, RP)* formulated clinical questions concerning the potential affected organs at risk after upper abdominal radiotherapy in WT and NBL patients (Supplementary Table S1). A systematic search was conducted of the English literature published between January 1990 and September 2023 using the PubMed database to answer these questions; although an initial search was also performed in SCOPUS, all identified articles overlapped with those in PubMed, which additionally yielded unique records, supporting the decision to proceed exclusively with PubMed (see Supplementary Table S2 for the full search strategy).

Eligibility criteria and study selection

All studies were independently screened by two reviewers (FW and FZ) using the ASReview screening aid which combines machine learning with expert input, prioritizing relevant articles based on user feedback [15]. Disagreements were resolved through consensus with a third reviewer (MH, GJ, RP). Predefined inclusion criteria concerned papers with pediatric patients diagnosed with WT or NBL, a minimum of five years of follow-up since the end of radiotherapy, and more than 10 patients. Studies were excluded if the radiotherapy prescription dose exceeded 36 Gy (as this dosage is irrelevant for current patients with WT and NBL undergoing radiotherapy), if they exclusively focused on [^{131}I] MIBG therapy or solely investigated late pulmonary irradiation toxicity. Additionally, narrative reviews were excluded (Supplementary Table S3).

Data extraction

Two authors (FW and FZ), as well as pediatric radiation oncologists members of the SIOPEN and SIOP-RTSG radiotherapy panels (BT, AL, TB, MG, PL, DJ, KD, SV, PM, BW, MA, AS, VG, HM and KB), independently reviewed all included papers and collected information on study design, treatment era, years of follow-up, participants, treatment, main outcomes, and additional remarks (Supplementary Table S4).

Assessment of risk of bias of individual studies

The Quality In Prognosis Studies (QUIPS) tool was used to assess the risk of bias in individual prognostic studies [16]. Using the QUIPS, a high-, moderate-, or low-risk of bias can be established in six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. This assessment was done by two independent reviewers (FW and FZ). Disagreements were resolved through consensus with a third reviewer (RP). Studies were categorized as low quality when they had a high-risk of bias. A color coding was used to indicate the considerations (red for lower quality, orange for medium quality, and green for higher quality).

Assessment of grading evidence across studies

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool was used to systematically assess the overall quality of evidence for each clinical question [17]. Recommended by the Cochrane Prognosis Methods Group, GRADE evaluates factors such as study design, study limitations, consistency, directness, precision, publication bias, effect size, dose–response, and plausible confounding. Grading was independently performed by FW and FZ, followed by consensus discussions, with a third reviewer (MH, GJ, or RP). The GRADE tool provides an overview of evidence quality for each organ at risk and its associated endpoints, categorized as very low, low, moderate, or high.

Results

Our search identified 3,080 records (Fig. 1). After screening titles and abstracts, 105 full-text articles were reviewed, of which 55 met our inclusion criteria. Five studies reported on risk factors for liver toxicity [18–22], 10 on vascular-metabolic/endocrine-pancreatic toxicity [8,23–31], one on vascular toxicity [32], 15 on renal toxicity [9,20,27,33–44], 13 on skeletal toxicity [10,39,45–55], 14 on secondary malignant neoplasms [28,38,49,56–66], one on spleen toxicity (67), and four on intestinal toxicity [22,38,39,68]. The QUIPS and GRADE results per study are described in Supplementary Tables S5 and S6. The summarized levels of evidence for increased toxicity are shown in Table 1 and Supplementary Table S7.

There is high level evidence indicating an increased risk of diabetes when radiotherapy doses exceed 10 Gy to the tail of the pancreas. This evidence is derived from 9 studies involving 8,074 patients treated with abdominal radiotherapy [8,23–30]. Moreover, upper abdominal radiotherapy resulted in a 15-fold increased risk of developing metabolic syndrome, although no dose–response relationship was reported for this outcome. This evidence is based on two studies with 85 patients treated with abdominal radiotherapy [23,24]. One study including 9,442 patients described that abdominal doses to the spleen exceeding 10 Gy were linked to a higher risk of (sub)lethal infections [67].

A moderate level of evidence is found for an increased risk of secondary malignant neoplasms, specifically colorectal (CRC) and renal cell carcinomas (RCC), following upper abdominal radiotherapy. One nested case-control study including 19 CCS with CRC, reported a 70 % increased risk of secondary CRC with each 10 Gy increment in dose [59]. Similarly, two studies, including 4,762 patients, described a dose–response relationship for RCC, with an increased risk observed at radiation doses ranging from 10 to 19.9 Gy [60,61]. Four studies, including 13,262 patients, observed that the risk of chronic kidney

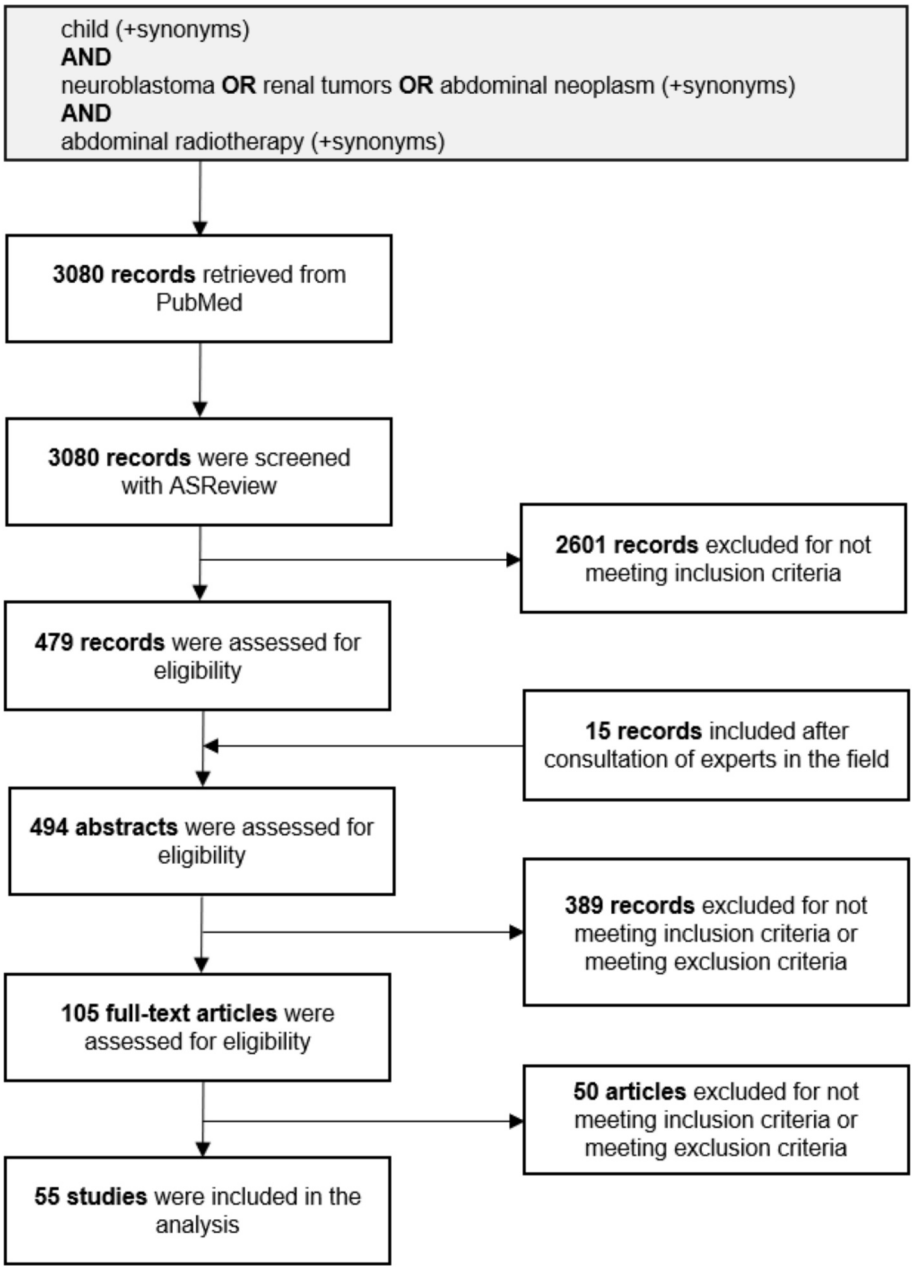

Fig. 1. Flowchart of study selection. This flowchart outlines the inclusion process for the systematic review, detailing study eligibility, exclusions, and final study composition.

Table 1
Summary of evidence table.

Level of evidence (GRADE)	Endpoints
⊕⊕⊕⊕ High	• Metabolic Syndrome • Diabetes • Functional asplenia
⊕⊕⊕⊖ Moderate	• SMN: Renal cell carcinomas, colorectal carcinomas • CKD / Decreased eGFR
⊕⊕⊖⊖ Low	• Portal hypertension • Proteinuria • Stature loss / growth disturbance • SMN: Skin cancer • Kidney transplantation
⊕⊖⊖⊖ Very low	• Focal nodular hyperplasia, any liver conditions, liver transplantation • BMI • Aortic growth • Tubular dysfunction, hypertension • Scoliosis, osteopenia • SMN: Leukemia, intestinal carcinomas (oesophagus, stomach, small intestine, colon excluding rectum, rectum/anus, hepatobiliary tree/pancreas, NOS), colorectal adenomas, general SMN • Intestinal obstruction, chronic diarrhea, upper GI ulcer, oesophageal disease, colitis

Abbreviations: BMI = body mass index; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; NOS = not otherwise specified; SMN = secondary malignant neoplasms; stature loss / growth disturbance = the failure to reach the target height and growth retardation.

disease (CKD) significantly increases with mean radiation doses exceeding 15 Gy [33,34,38,39].

For several conditions there is low level of evidence for the association with upper abdominal radiotherapy. Portal hypertension was reported in one study with 17 patients, with an increased risk observed after radiation doses of 15 Gy to the liver [18]. Proteinuria was evaluated in three studies involving 663 patients, with risks increasing significantly at mean doses exceeding 30 Gy to the kidney [34,36,37]. Additionally, five studies involving 1,504 patients highlighted the occurrence of stature loss or growth disturbances [10,51–54]. Growth disturbances are observed following doses of 15 Gy [45]. While no specific dose threshold was identified for skin cancer, one study involving 2,308 patients found a significant association between upper abdominal radiotherapy and an elevated risk of skin cancer [56].

The increased risk for endpoints such as focal nodular hyperplasia of the liver, various liver conditions, aortic growth, osteochondroma, osteopenia, leukemia, intestinal carcinomas, colorectal adenomas, chronic diarrhea, upper gastrointestinal ulcers, esophageal disease, and colitis, is supported by a very low level of evidence [19,22,32,55,57,58,62]. All were evaluated in only one study that met our inclusion criteria. In contrast, there is more than one study available for endpoints such as Body Mass Index (BMI), tubular dysfunction, arterial hypertension, scoliosis or spinal deformity, general secondary malignant neoplasms, and intestinal obstruction [21,27,29,31,35,37,39,40,44–50,69]. However, these studies were scored low on quality, often due to small sample sizes and a descriptive nature. For example, the available literature on scoliosis consists of seven studies encompassing a total of 197 patients [39,45–50].

In addition, patient- and treatment-related variables associated with late effects were identified. The most significant treatment-related variable is chemotherapy (n = 19 studies) [18,20,22,26,33–37,44,56,58–63,65,67], while the most significant patient-related variable found was age at diagnosis (n = 9 studies) [10,22,26,31,52,56,63,66,69]. The association of patient and treatment related variables is shown in Table 2.

Discussion

This systematic review highlights the levels of evidence for late toxicities associated with upper abdominal radiotherapy in CCS treated for WT and NBL. High and moderate levels of evidence are available for an increased risk of radiotherapy-induced diabetes, metabolic syndrome, functional asplenia, SMN such as CRC and RCC, and CKD. On the other hand, only low and very low levels of evidence exist for late effects such as scoliosis, spinal deformities, vascular growth abnormalities besides a long list of other toxicities.

The association between abdominal radiotherapy and the increased risk of diabetes/metabolic syndrome is supported by a high level of evidence, yet it remains underrecognized in clinical practice. Metabolic syndrome contains a cluster of cardiovascular risk factors, including abdominal adiposity, insulin resistance, dyslipidemia, and arterial hypertension [24]. This finding is clinically relevant, as patients with metabolic syndrome are three times more likely to develop cardiovascular disease and have a two- to five-times higher risk for diabetes [61].

Table 2
Patient- and treatment variables associated with late toxicities.

Endpoint	Ref	Level of evidence (GRADE)	Radiotherapy	Chemotherapy	Surgery	Age at diagnosis	Sex
Portal hypertension	[18]	⊕⊖⊖⊖	Y	Y	NS	NS	No
Focal nodular hyperplasia	[19]	⊕⊖⊖⊖	I	NS	NS	NS	NS
Liver transplantation	[20,21]	⊕⊕⊖⊖	No, I	Y, NS	NS, NS	NS, NS	No, NS
Any liver conditions*	[22]	⊕⊖⊖⊖	Y	Y	Y	Y	NS
Metabolic syndrome	[23,24]	⊕⊕⊕⊕	Y, Y	NS, NS	N, NS	NS, NS	NS, NS
Diabetes	[8,23,24,25,26,27,28,29,30]	⊕⊕⊕⊕	Y, Y, Y, N, Y, N, Y, Y, I	NS, NS,Y, NS, N, NS, NS, NS, NS	NS, NS, N, N, N, NS, NS, NS, NS	NS, NS, Y, NS, NS, NS, NS, NS, NS	NS, NS, N, NS, NS, NS, NS, NS, NS
Body mass index	[27,31]	⊕⊖⊖⊖	N, N	NS, N	NS, NS	NS, Y	NS, N
Hypertension	[21,27,37,40,44,69]	⊕⊖⊖⊖	Y, N, N, Y, N, I	N, NS, NS, NS, N, NS	N, NS, NS, NS, NS, NS	Y, NS, NS, NS, N, NS	Y, NS, NS, NS, N, NS
Aortic growth	[32]	⊕⊖⊖⊖	Y	NS	NS	NS	NS
Chronic kidney disease	[33,34,38,39]	⊕⊕⊖⊖	Y, Y, N, I	Y, Y, N, NS	Y, Y, NS, NS	N, NS, NS, NS	N, NS, NS, NS
Tubular dysfunction	[35,37]	⊕⊖⊖⊖	N, N	Y, Y	N, N	NS, NS	N, NS
Proteinuria	[34,36,37]	⊕⊕⊖⊖	N, Y, N	NS, Y, Y	Y, N, N	NS, NS, NS	N, NS, NS
Decreased eGFR	[9,27,36,40,41,42,43,44]	⊕⊕⊕⊖	Y, Y, Y, Y, Y, Y, Y, N	Y, NS, NS, NS, N, NS, NS, Y	Y, Y, NS, NS, NS, NS, NS, NS	Y, Y, NS, NS, NS, NS, NS, N	N, NS, NS, NS, NS, NS, NS, Y
Kidney transplantation	[20]	⊕⊕⊖⊖	Y	Y	Y	N	NS
Spinal deformity (MSA)	[39,45,46,47,48,49,50]	⊕⊖⊖⊖	Y, I, I, I Y, I, N	NS, NS, NS, NS, NS, NS, NS	NS, NS, NS, NS, NS, NS, NS	NS, NS, NS, NS, NS, NS, NS	NS, NS, NS, NS, NS, NS, NS
Stature loss/growth disturbance	[10,51,52,53,54]	⊕⊕⊖⊖	Y, Y, Y, Y, I	N, NS, NS, NS, NS	NS, NS, NS, NS, NS	Y, NS, Y, NS, NS	NS, NS, Y, NS, NS
Osteopenia/porosis	[55]	⊕⊖⊖⊖	N	NS	NS	NS	NS
Skin cancer	[56]	⊕⊕⊖⊖	Y	Y	No	Y	Y
Leukemia	[57]	⊕⊖⊖⊖	N	NS	NS	NS	NS
Intestinal carcinomas	[58]	⊕⊖⊖⊖	Y	Y	NS	NS	NS
Renal cell carcinomas	[60,61]	⊕⊕⊕⊕	Y, Y	Y, Y	NS, NS	N, N	NS, N
Colorectal carcinoma	[59]	⊕⊕⊕⊕	Y	Y	NS	NS	NS
Colorectal adenomas	[62]	⊕⊖⊖⊖	Y	Y	NS	NS	NS
SMN in general	[28,38,49,63,64,65,66]	⊕⊖⊖⊖	Y, N, I, Y, Y, N, I	Y, N, NS, Y, N, NS, NS	NS, NS, NS, NS, NS, NS, NS	Y, NS, NS, NS, Y, NS, NS	Y, NS, N, NS, Y, NS, NS
(Sub)lethal infections	[67]	⊕⊕⊕⊕	Y	Y	Y	N	N
Intestinal obstruction	[38,39,68]	⊕⊖⊖⊖	Y, Y, N	N, NS, NS	N, NS, NS	N, NS, N	N, NS, N
Upper GI complications**	[22]	⊕⊖⊖⊖	Y	Y	Y	Y	NS
Lower GI complications***	[22]	⊕⊖⊖⊖	Y	Y	Y	Y	NS

Abbreviations: I = inconclusive; Y = yes; N = no; NS = not specified; All abbreviations correspond to the order of references.
* Gallstone and other gall bladder issues, liver cirrhosis, jaundice, liver biopsy, other liver trouble.
** Ulcer, esophageal disease, indigestion/heartburn, nausea/vomiting, other upper GI trouble.
*** Intestinal polyps/diverticular disease, colitis, constipation, diarrhea, rectal/anal fistula/stricture/other obstruction surgery, colostomy/ileostomy, other lower intestinal trouble.

Abdominal radiotherapy can damage the endocrine and metabolic function of the pancreas, liver, and kidneys, causing insulin resistance, dyslipidemia, and arterial hypertension. Additionally, it can alter body composition by increasing visceral fat accumulation, further elevating the risk of dyslipidemia, as well as diabetes, and thus contributing to metabolic syndrome [24,70]. Recent studies have shown that radiation to the pancreatic tail increases the risk of diabetes, particularly in the age group in which WT and NBL are typically diagnosed. At age 45, de Vathaire et al. reported a 16 % cumulative incidence of diabetes among 511 patients who received > 10 Gy to the pancreatic tail using two anterior-posterior/posterior-anterior (AP/PA) beams in a 2D-era [8]. Similarly, Friedman et al. described a fivefold increased risk of diabetes in those diagnosed at age 1 receiving 10–19.9 Gy, compared to a threefold risk in those diagnosed at age 5. In contrast, no significant increased risk was noted in patients diagnosed at 15 years or older [25]. Therefore, radiotherapy protocols should prioritize dose constraints to the pancreatic tail, ideally keeping exposure below 10 Gy. Uncertainties remain regarding the precise mechanisms that explain the association between radiation and diabetes. While this risk appears to be dose-dependent, with a plateau observed between 20–29 Gy, it primarily manifests in adulthood. The diabetes that develops is not classic type 1 diabetes characterized by insulin deficiency, but rather resembles type 2 diabetes, which is mainly driven by insulin resistance [71]. Abdominal fat tissue plays an important role in regulating insulin sensitivity, and both visceral and subcutaneous fat depots often lie within the radiation field. In obesity, insulin resistance worsens not merely due to an increased number of adipocytes, but more significantly when adipocytes are hypertrophy. Although new adipocyte formation can accommodate some lipid storage, hypertrophic adipocytes have limited capacity to store additional lipids. As a result, excess lipids accumulate in the liver, contributing to fatty liver disease, dyslipidemia, and insulin resistance. Therefore, it may be plausible that damage to the “flexibility” of abdominal fat depots is a key factor linking radiation exposure to the association with diabetes mellitus [72]. Additionally, studies have shown that both insulin-dependent and non-insulin-dependent diabetes (type 2) are observed after pancreatic irradiation, reinforcing the notion that radiation-induced β-cell dysfunction may not exclusively mimic type 1 diabetes [71]. Higher doses of radiotherapy, particularly above 20 Gy, significantly increase the risk of hypertension, underscoring the importance of kidney-specific dose constraints [12].. To date, no dose constraints have been established for abdominal fat and the liver in relation to fat metabolism. Similarly, a dose constraint may also be advised for the spleen. Weil et al. found that among 9,442 survivors who received splenic radiation, the cumulative incidence of late infection-related mortality at 35 years was 0.6 %. Even moderate doses of 10–19 Gy to the spleen were associated with a 5.5-fold increase in the risk of late infection-related mortality [67]. To reduce the risk of mortality from overwhelming post-radiation hyposplenic infection, the mean dose should be limited to 10 Gy, if not achieved the need for antibiotic prophylaxis and/or (re)vaccination should be considered [73]. Specific recommendations include: (1) Vaccines should ordinarily be administered as soon as practicable after recognition of non-surgical hyposplenism; (2) Survivors with functional hyposplenism should receive vaccines against Streptococcus pneumoniae and Neisseria meningitidis, along with annual influenza immunization; (3) Antibiotic prophylaxis remains crucial, as current vaccines do not provide full coverage for all pneumococcal serotypes or meningococcal strains. In high-risk patients, this may include lifelong prophylaxis with oral penicillin’s or macrolides; (4) Patients not at high risk should be counselled regarding the available evidence for the risks and benefits of lifelong antibiotics and may choose to discontinue them; (5) All patients should carry a supply of appropriate rescue antibiotics for emergency use [74].

A Moderate level of evidence supports the association between upper abdominal radiotherapy and SMN, particularly CRC and RCC. Heymer et al. reported that among 69,460 five-year CCS, diagnosed between 1940 and 2008, 143 developed CRC between the ages of 30 and 70. Those treated with abdominal radiotherapy were three times more likely to develop CRC. In survivors treated with > 30 Gy to the planning target volume (PTV), the cumulative absolute risk of CRC by age 50 was 1.14 %/1.08 %, in male/female survivors respectively, compared to the 0.27 % risk expected in the general population [75]. Over 75 % of the survivors in this study were treated before 1980, suggesting the use of AP/PA radiotherapy. For decades, this conventional two-opposing photon beams were the standard for covering the abdominal target volumes in WT and NBL. However, the increasing use of highly conformal target volumes combined with modern photon techniques have significantly reduced the mean dose to the bowel (far) below 10 Gy in most of the cases [76]. This suggests that the CRC risk between patients treated with or without abdominal radiotherapy, which was already low, may now be even lower with the use of modern radiotherapy modalities be it photons or protons. In contrast, modern radiotherapy solutions only have a modest impact on the kidney(s) dose given the location of the target volume often including a rim of normal kidney tissue within the planning target volumes. Based on a cohort of 4,350 survivors treated before 1985, of whom 13 developed RCC, de Vathaire et al. suggested that RCC risk increases even with moderate radiation doses (2–5 Gy) to the kidney. Importantly, only 3 of these survivors with RCC received doses of less than 10 Gy, indicating that the absolute risk remains exceptionally low [60]. Given this, while minimizing kidney dose remains a priority in radiotherapy protocols, it is crucial to recognize that the actual risk of RCC, even with moderate doses, is still quite low. Similarly, the PENTEC examined the risk for CKD and concluded that renal toxicity from a fractionated dose of 10.5 Gy in seven fractions to the whole abdomen was low, with less than a 5 % chance of chronic moderate (GFR = 30–59 mL/min/1.73 m^2) or severe toxicity (GFR = 15–29 mL/min/1.73 m^2) [12].

For several endpoints, the level of evidence is (very) low. It is important to distinguish between endpoints where the (very) low evidence arises from high-quality studies with inconsistent results and limited generalizability, often due to a lack of focus on WT and NBL specifically, such as intestinal obstruction [38,39,68], and those where the evidence comes from multiple studies that are outdated, based on small sample sizes, and provide mostly descriptive results, such as scoliosis [39,45–50]. Although upper abdominal radiotherapy has been a well-known risk factor for severe scoliosis, we found that the available evidence does not offer clear guidance for clinical practice. To address this gap, expert pediatric radiation oncologists have recently proposed recommendations for dose prescriptions to target volumes adjacent to the vertebrae, aiming for greater uniformity in daily practice. For children within the typical diagnostic age range of WT and NBL, Hoeben et al. recommend a homogeneous dose in the left–right and posterior-anterior directions to prevent asymmetrical growth. If dose inhomogeneity is unavoidable, the gradient should be limited to less than 3 Gy for children < 2 and less than 5 Gy for children aged 2 years to the end of the pubertal growth acceleration phase, for tumor prescription doses up to 40 Gy [77]. Despite the (very) low level of evidence for scoliosis, these recommendations could be considered in treatment planning to balance efficacy with long-term toxicity reduction.

This is the first comprehensive overview of evidence on radiotherapy-induced late toxicities in CCS from WT and NBL. However, some limitations are important to stress. First, this systematic review showed that the quality of the available literature on this subject, as assessed by the GRADE tool, is limited. Although our search starting with literature from 1990 revealed plenty of studies, most of them are observational. Randomized controlled trials (RCTs) comparing radiotherapy with other treatment modalities, as radiotherapy cannot always simply be omitted, rather different radiation doses, volumes and techniques would provide a more definitive understanding of cause-and-effect relationships. However, when it comes to dose–response relationships, there is stronger evidence for causality. This is why the studies investigating dose–response relationships were rated higher in the GRADE tool, reflecting a higher level of evidence. This decision-

Table 3
Current and future strategies to reduce the risk of late effects.

Current strategies to avoid late toxicities	Future strategies to mitigate late toxicities
• 3D/4D-based treatment planning • Highly conformal target volumes • IMRT/VMAT and proton therapy • Image-guided radiotherapy • Organ constraints • Standardizing vertebral body coverage • Evaluation of lower radiotherapy doses • Randomized trial to evaluate the role of boost dose in patients with a residue • Prospective quality control of volumes and doses by peers • Supportive treatment	• Adaptive radiotherapy • Randomized trials to evaluate the safety of reduction of prescription dose • Biological predictors of radiotherapy response • Biological predictors in cancer predisposition syndromes to avoid radiotherapy late effects • Biological predictors before and during multimodal treatment to evaluate the need for dose escalation or de-escalation • Auto contouring with AI tools

Abbreviations: IMRT = Intensity-Modulated Radiotherapy; VMAT: Volumetric Modulated Arc Therapy.

making process is therefore factored into the scoring. Second, half of the included studies were not specific to WT or NBL but rather encompassed heterogeneous CCS cohorts. We mitigated this issue by focusing on studies that specifically addressed upper abdominal radiotherapy and provided detailed information on the number of patients treated.

The radiotherapy panel recommends several preventive strategies to mitigate the risk of late effects for survivors of upper abdominal radiotherapy. These include the use of highly conformal target volumes in combination with modern technologies like (online) adaptive approaches either by photons or protons. Further efforts should focus on reducing radiotherapy prescription doses within the context of prospective studies. In addition, identifying biological predictors of (individual) radiotherapy response of tumor cells and the more challenging organs at risk could enable more personalized treatment approaches, optimizing the therapeutic efficacy. These recommendations are shown in Table 3.

This systematic review highlights the different levels of evidence for a list of late toxicities associated with upper abdominal radiotherapy in CCS with Wilms tumor and neuroblastoma. Although dose reductions and improved ballistics have already contributed to mitigating the risk of some late effects, there remains scope for innovation to minimize toxicities further.

Consent for publication

Not applicable.

CRediT authorship contribution statement

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Ethics approval and consent to participate

Not applicable.

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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.2025.110961.

Data availability

All data generated or analyzed during this study are included in this

published article [and its supplementary information files].

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