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PENTEC ORGAN SYSTEM REVIEW

Liver Late Effects in Childhood Cancer Survivors Treated With Radiation Therapy: A PENTEC Comprehensive Review

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Purpose: A pediatric normal tissue effects in the clinic (PENTEC) comprehensive review of patients with childhood cancer who received radiation therapy (RT) to the liver was performed to develop models that may inform RT dose constraints for the liver and improve risk forecasting of toxicities.

Methods and Materials: A systematic literature search was performed to identify published data on hepatic toxicities in children. Treatment and outcome data were extracted and used to generate normal tissue complication probability (NTCP) models. Complications from both whole and partial liver irradiation were considered. For whole liver irradiation, total body irradiation and non−total body irradiation treatments were considered, but it was assumed that the entire liver received the prescribed dose. For partial liver irradiation, only Wilms tumor flank field RT could be analyzed. However, a prescribed dose assumption could not be applied, and there was a paucity of analyzable liver dosimetry data. To associate the dose-volume exposures with the partial volume complication data from flank irradiation, liver dose-volume metrics were reconstructed for Wilms tumor flank RT using age-specific computational phantoms as a function of field laterality and superior extent of the field.

Results: The literature search identified 2103 investigations pertaining to hepatic sinusoidal obstructive syndrome (SOS) and liver failure in pediatric patients. All abstracts were screened, and 241 articles were reviewed in full by the study team. A model was developed to calculate the risk of developing SOS after whole liver RT. RT dose ($P = .006$) and receipt of nonalkylating chemotherapy ($P = .01$) were significant. Age <20 years at time of RT was borderline significant ($P = .058$). The model predicted a 2% risk of SOS with zero RT dose, 6.1% following 10 Gy, and 14.5% following 20 Gy to the whole liver (modeled as the linear-quadratic equivalent dose in 2-Gy fractions [$\alpha/\beta = 3$ Gy]). Patients with Wilms tumor treated with right flank RT had a higher observed rate of SOS than patients receiving left flank RT, but data were insufficient to generate an NTCP model for partial liver irradiation. From the phantom-based dose reconstructions, mean liver dose was estimated to be 2.16 ± 1.15 Gy and 6.54

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± 2.50 Gy for left and right flank RT, respectively, using T10-T11 as the superior field border and a prescription dose of 10.8 Gy (based on dose reconstruction). Data were sparse regarding rates of late liver injury after RT, which suggests low rates of severe toxicity after treatment for common pediatric malignancies.

Conclusions: This pediatric normal tissue effects in the clinic (PENTEC) review provides an NTCP model to estimate the risk of hepatic SOS as a function of RT dose following whole liver RT and quantifies the range of mean liver doses from typical Wilms tumor flank irradiation fields. Patients treated with right flank RT had higher rates of SOS than patients treated with left flank RT, but data were insufficient to develop a model for partial liver irradiation. Risk of SOS was estimated to be approximately ≤6% in pediatric patients receiving whole liver doses of <10 Gy.

Introduction

Selected pediatric malignancies of the abdomen and pelvis are often treated with radiation therapy (RT), including neuroblastoma, Wilms tumor, lymphoma, rhabdomyosarcoma, and other malignancies. In 2010, Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) published a series of organ site papers to evaluate dose-volume constraints associated with liver toxicity in adults.[1] Limited data exist on the dose-volume effects of RT on the liver in children. The purpose of this systematic review was to evaluate the published data regarding the risk of hepatic sinusoidal obstructive syndrome (SOS) and liver failure in children following anticancer therapy and generate normal tissue complication probability (NTCP) models specific to this endpoint where practical. These results will help to quantify the risks associated with the delivery of curative intent RT and provide guidance to providers on mitigating these risks.

Clinical Significance

In 2021, an estimated 15,590 children and adolescents (age <20 years) received cancer diagnoses.[2] RT is used to treat a variety of abdominal and pelvic malignancies, spanning a wide range of field sizes and doses and leading to variable exposure of the liver to RT. For example, patients with unresectable rhabdomyosarcoma, Ewing sarcoma, or osteosarcoma may receive high dose focal RT to doses of ≥45 Gy. Selected patients with Hodgkin lymphoma or high-risk neuroblastoma may be treated to focal fields with intermediate doses of 20 to 30 Gy.[3] Selected patients with Wilms and other renal tumors, leukemia receiving total body irradiation, and tumors having a high risk of intraperitoneal spread (eg, desmoplastic small round cell tumor of the abdomen), may receive flank or whole abdominal irradiation. Finally, patients with central nervous system tumors treated with craniospinal irradiation using photon-based techniques may have low to moderate dose exposure to the abdominal organs, including the liver.

The liver is responsible for glycogen storage, synthesis of plasma lipoproteins, albumin, prothrombin, and fibrinogen, nutrient and drug metabolism, bile secretion, and elimination of wastes. It also has the unique ability to regenerate following injury and partial hepatectomy, producing new functional tissue in response to insult.

Liver function after surgery and implications for volume effects

Understanding the tolerance of the liver to partial resection may have implications for refining RT dose-volume-outcome relationships. Partial hepatectomy is considered the standard of care in the management of primary and metastatic liver tumors. The incidence of posthepatectomy liver failure (PHLF) ranges from 0% to 32% in published series and increases with more extensive resections involving >2 segments and underlying liver disease.[4] The volume of residual functional liver following surgery is important for predicting postoperative PHLF. In the absence of chronic liver disease, the estimated limit for safety ranges from 20% to 30% of residual healthy liver.[5-8] In 301 patients treated with extended right hepatectomy, patients with a remaining functional liver reserve of <20% had significantly higher rates of PHLF and death (34% and 11%, respectively) compared with patients with a 20% to 30% reserve (10% and 3%, $P < .001$ and $P < .05$, respectively).[9] No significant difference in the rates of PHLF and death were observed in patients with a 20% to 30% versus >30% functional liver reserve. The absolute minimum safe limit for liver resection is considered 20% of total liver volume in patients without underlying liver disease.[10]

While the literature on preoperative assessment of functional liver reserve is largely derived from adult data, published series suggest comparable safety in assessing pediatric patients for hepatectomy. Li et al[11] reported on 87 pediatric patients treated with hepatectomy between 2010 and 2018, with 59% receiving major resections of ≥3 segments. In total, 16.1% of patients developed complications, only 2 of which were grade 3 and with no postoperative deaths. The authors concluded that major liver resections in children were not associated with an increased risk of postoperative complications.[11] These data suggest that sparing a sufficient volume of normal liver is associated with recovery of liver function following surgery. This knowledge may help to better understand the incidence of toxicities following liver RT as a function of volume.

SOS

Hepatic SOS is a subacute toxicity that can occur in patients treated with chemotherapy, hematopoietic stem cell transplantation (HSCT), and/or RT.[12] SOS arises from damage

to small hepatic vessels, leading to endothelial cell swelling, narrowing of the hepatic venules, and partial or complete occlusion of the small veins within the liver. Based on this pathogenesis, SOS was previously named hepatic veno-occlusive disease.[13] This occlusion can lead to hypoxic cell death, necrosis, and liver atrophy. Patients frequently present with jaundice, painful hepatomegaly, and ascites.[14] SOS often requires specialized hospital care. Mortality is <5% in patients with mild disease severity but rises to 80% in patients with severe disease and multiorgan failure.[15]

In QUANTEC, the risk of radiation-induced SOS was estimated to be ≤5% with whole liver doses of ≤30 Gy and ≤28 Gy (at 2 Gy per fraction) in patients with liver metastases and primary liver tumors, respectively. Notably, most data in QUANTEC derived from partial liver irradiation were converted to mean dose (via the Lyman Kutcher Burman Model).[1] Pre-existing liver dysfunction and cirrhotic liver disease are known contributing risk factors for SOS.[16,17] In adults, higher doses can safely be delivered with partial liver irradiation (eg, with SABR), provided that an acceptable portion of the liver is spared.

SOS also occurs in patients with pediatric and hematologic malignancies in the absence of RT. Established risk factors include allogeneic or autologous HSCT, selected systemic therapies (oxaliplatin, 5-fluorouracil, gemtuzumab ozogamicin, and inotuzumab ozogamicin),[18] hepatic iron overload, acute or chronic hepatitis, and other severe liver injuries. In patients undergoing HSCT, unrelated donor transplants, early engraftment, and post−stem cell infusion sepsis are associated with an increased risk of SOS.[19-21] Systemic therapies and other SOS risk factors may be synergistic with the effect of RT.[22] To date, no clear studies have evaluated the risk of SOS with RT dose in pediatric cancer patients and the impact of other variates.

Medical management for SOS is supportive. The only approved drug therapy for SOS is defibrotide,[23] which has also been used for prophylaxis in very high-risk patients, but its use in this capacity is limited owing to high cost.[24,25] Ursodeoxycholic acid with and without corticosteroids has also been used for prophylaxis, with unclear efficacy.[26-28] Supportive care measures include careful fluid balance maintenance and nutrition as well as avoidance of hepatotoxic drugs. After HSCT, medical prophylaxis with ursodeoxycholic acid has been reported but is not labeled for this indication, and proof of efficacy is limited.[10] Some patients will recover, but SOS can be fatal. Therefore, objective data regarding the risk of SOS following therapeutic RT is of significant interest.

Endpoints and Toxicity Scoring

For this review, the primary endpoint was the incidence of hepatic SOS after RT. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 scores liver dysfunction as jaundice (grade 2), asterixis (grade 3), encephalopathy/coma (grade 4), and death (grade 5).[29] Most reports in the literature, however, did not grade toxicity according to these criteria, and fortunately, death is rare following RT. In this analysis, SOS was defined using the McDonald criteria, namely jaundice (bilirubin >27 mmol/L), hepatomegaly, and ascites/weight gain,[6] which were consistent with the published literature. SOS generally occurs within 3 months following the causative exposure, which for this population may occur at any time point during active treatment. Improvement in liver function is expected following recovery from SOS. To mitigate potential overlap with SOS, chronic liver injury was defined as an elevated alanine aminotransferase above normal at any time ≥1 year following treatment. Sufficient data were only available for dose response modeling for SOS following whole liver irradiation. Limited data were available for SOS following partial liver irradiation and chronic liver injury.

The Child-Pugh score has been used to assess liver dysfunction in adults based on clinical and laboratory values and is frequently used in patients with cirrhosis. Although chronic liver dysfunction is common in patients with hepatocellular carcinoma,[16] cirrhosis and liver dysfunction are uncommon in children. As a result, this classification schema was not used.

Anatomy and Developmental Dynamics

The liver is composed of 4 lobes and can also be divided into 8 functionally independent segments, each of which is composed of thousands of smaller lobule subunits. Lobules are connected through a network of progressively enlarging tubules that ultimately form the common hepatic duct, which is responsible for transporting bile from the liver into the gallbladder and duodenum. The liver is supplied by 2 distinct blood sources; it receives oxygenated blood from the hepatic artery and nutrient-rich blood via the portal vein. Each liver segment has its own arterial, venous, and biliary drainage systems, such that elimination of 1 or more liver segments does not compromise the function of the remainder.

The liver is the only visceral organ with the capacity to regenerate in response to chemical injury and partial hepatectomy.[30] Multiple signaling pathways are upregulated in remaining hepatocytes within minutes after partial hepatectomy, and the proliferation of hepatocytes and other liver cell types is controlled by multiple key substrates for cell division, including the MET gene, the epidermal growth factor receptor, and the phosphoinositide 3-kinase/Akt pathways.[31] Interestingly, this cell proliferation is not dependent on liver progenitor cells and derives from existing terminally differentiated cells. Existing hepatocytes and cholangiocytes can transdifferentiate into the other cell type if proliferation of the other is impaired, such as in the setting of cirrhosis, and can function as a facultative stem cell. In the healthy liver, hepatocyte cell turnover is slow, but in chronic liver disease, ongoing cell death and regeneration can lead to fibrosis, cirrhosis, and increased rates of carcinogenesis. Chronic liver disease is much less common in children than

in adults, but preoperative evaluation of posthepatectomy liver function and morbidity are still important in decision-making.[32]

Defining Volumes

The liver can be readily delineated on computed tomography (CT). The radiation planning CT scan should include the entire liver, which should be delineated as an organ at risk for accurate dosimetry and risk assessment in patients in whom the liver is incidentally or purposefully irradiated. In patients with disease involving the liver, magnetic resonance imaging with contrast is recommended for image fusions to better define the gross tumor volume/clinical target volume when partial liver treatment is planned. Given that the liver is mobile and deformable, image registration can be challenging and is often imperfect; priority should generally be given to optimizing image registration in the vicinity of the gross tumor volume.

Review of Dose-Volume Response Data and Risk Factors

A systematic literature search was performed to identify all published data on hepatic toxicities in children treated with RT in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses principles.[33] PubMed and Cochrane Library searches of peer-reviewed articles written in English and published between January 1, 1995, and October 2, 2017, were conducted. Search criteria were developed (by C. M.R., J.A.B., and L.S.C.) to identify studies that evaluated the effect of RT on the risk of liver toxicities in pediatric patients with cancer. The literature search identified 2103 investigations pertaining to hepatic SOS or liver failure in pediatric patients. Appendix E1 details the search strategy, abstract selection, bias assessment, and data collection.

Two investigators (M.D.H. and J.A.B.) independently reviewed the titles and abstracts of the 2103 abstracts that were selected. Full text articles were reviewed by the same investigators for all articles that were considered potentially germane. Review of the published data demonstrated that sufficient data were available to model the incidence of hepatic SOS after whole liver and partial liver RT. The investigators (M.D.H. and J.A.B.) extracted data on each patient cohort, including patient ages, tumor biology, RT, chemotherapy, and incidence of hepatic SOS, into an electronic database from all eligible studies. Papers were included if they provided data on the incidence of SOS in patients treated for pediatric malignancies who were treated with either whole or partial liver RT (without boost) and where data on dose, fractionation, chemotherapy, and patient age distribution were available. A strict upper age limit was not established for the age of patients to be included; however, at least 50% of the patient series had to be children or adolescents. Articles reporting SOS incidence in patient series with <10 patients were excluded. Data extraction was performed for study data that met the criterion for inclusion and had a low assessment of potential bias (discussed in the following sections; also see Appendix E2).

Whole liver results

From 2103 abstracts, 241 articles were reviewed in full. Of those, 13 papers reported SOS outcomes following whole liver RT on 1299 patients with a median age <40 years. The prescribed doses ranged from 5 to 36 Gy. Patient series where no RT was given but SOS was reported were included; these chemotherapy-only series were treated as zero RT dose regimens. Figure 1 summarizes the selection and elimination process used to identify eligible studies. Table 1 summarizes the article data included for analysis of SOS following whole liver RT. Selected articles reported SOS outcomes for distinct patient cohorts treated to different whole liver RT doses, and these cohorts from the same article are listed separately from one another in Table 1.

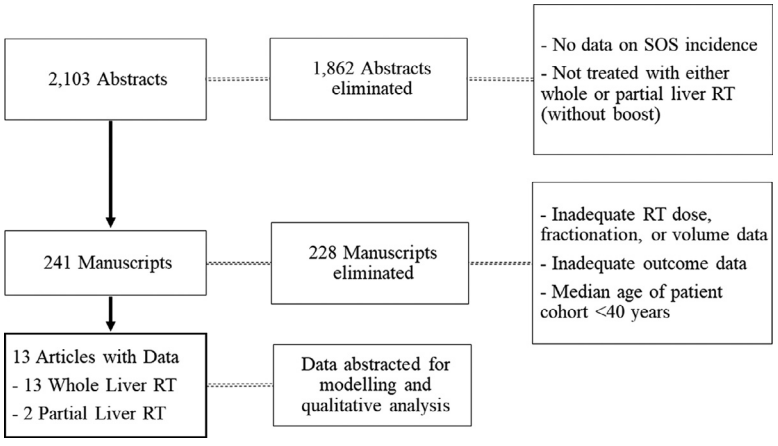

Fig. 1. CONSORT (Consolidated Standards of Reporting Trials) diagram summarizing the selection and elimination of published data from our systematic literature search to identify articles reporting the incidence of sinusoidal obstructive syndrome (SOS) as a function of radiation dose. *Abbreviation:* RT = radiation therapy.

Table 1 Data used for modeling risk of hepatic SOS following whole liver irradiation

First author	Year	n	Dose	d/fx	Median age	Diagnosis	TBI	SOS incidence
Dufour[45]	2001	22	5	5	6.3	Mixed	Yes	13.6%
Druley[46]	2009	55	5.5	5.5	11.8	Mixed	Yes	5.5%
Chou[47]	1996	15	7	7	1.2	SCID	Yes	26.7%
Flentje[22]	1994	18	7.5-27	1.5	3.8	Wilms	No	0.0%
Balduzzi[48]	2002	636	12	2	8	Leukemia	Yes	4.9%
Bredeson[49]	2013	46	12	2	8.6	Leukemia	Yes	13.0%
Bredeson	2013	23	12	2	9.6	Leukemia	Yes	8.7%
Chou	1996	58	12	2	8.4	Leukemia	Yes	22.4%
Tefft[44]	1977	19	19.5-36	1.5	2	Wilms	No	10.0%-66.7%
Ganem[50]	1988	155	10	10	24	Leukemia	Yes	11.0%
Girinsky[51]	2000	73	10	10	30	Leukemia	Yes	13.7%
Altschuler[52]	1989	32	11	2.2	23.5	Leukemia	Yes	6.3%
Gutierrez-Delgado[53]	2003	42	12	1.5	38	Hodgkin	Yes	2.4%
Kalayoglu-Besisik[54]	2005	17	12	2	33	Mixed	Yes	0.0%
Girinsky	2000	74	14.85	1.35	31	Leukemia	Yes	4.1%
Levitt[55]	1984	14	20	1	25	Hodgkin	No	7.1%

All data in the patient populations are as reported in each study or calculated from the data.
Abbreviations: d/fx = dose per fraction; n = sample size; SCID = severe combined immunodeficiency; SOS = sinusoidal obstructive syndrome; TBI = total body irradiation.

The primary endpoint of interest was incidence of SOS, defined by the McDonald criteria (bilirubin >27 mmol/L, hepatomegaly, and ascites/weight gain).[6] A weighted generalized linear model with a logit link was used to model whole liver data for the incidence of SOS (performed by A.J.). RT dose was modeled as the linear-quadratic equivalent dose in 2 Gy per fraction (EQD2) assuming an $\alpha/\beta = 3$ Gy to compare studies with different doses per fraction. Variables were included based on the results of a stepwise regression and other variables that were reported in the literature to be associated with increased risk of SOS. The final model contained only statistically significant variables ($P < .05$). Since these data were derived in the setting of whole liver RT, we assumed the reported dose to be a reasonable approximation of a uniform dose delivered to the liver.

RT dose ($P = .006$) and use of nonalkylating chemotherapy (defined as cytarabine, methotrexate, fludarabine, anthracyclines, topoisomerase inhibitors, vinca alkaloids, bleomycin, and dactinomycin) ($P = .01$) were significantly associated with SOS. Age <20 years at time of RT was borderline significant ($P = .058$). To further assess if the effect of RT differed in younger versus older ages, we also performed a subgroup analysis where the model was rerun using only studies with patients with a median age <20 and then ≥20 years. In this inquiry, RT dose remained significant in the model when only studies with patients with a median age <20 and ≥20 years were included ($P = .02$ and $P = .02$, respectively).

Figure 2 illustrates the dose-response function with the SOS complication rate plotted as a function of equivalent dose in 2-Gy fractions. Patient series were plotted as discrete points with the area scaled according to the number of patients included in each series. SOS risk at zero RT dose was approximately 2%. In patients <20 years of age, the model-predicted SOS rates after whole liver doses of 10 Gy and 20 Gy were 6.1% and 14.5%, respectively.

The whole liver doses (at 2 Gy per fraction) associated with a 5% risk of SOS in patients <20 years old and ≥20 years old were 8 Gy and 14 Gy, respectively.

Several chemotherapy agents, including dactinomycin, busulfan, mercaptopurine, and methotrexate, have been implicated in the development of late liver toxicity.[34] We extracted the individual chemotherapy agents received by patients in each series in this data set and analyzed the effect of individual chemotherapy agents on the risk of SOS. We specifically analyzed the effect of dactinomycin and other agents and did not find a significant relationship between any specific cytotoxic agent and SOS risk. Treatment with HSCT was also not significant. In this analysis, only when nonalkylating chemotherapy agents were binned together was a significant effect observed. While this suggests that 1 or more chemotherapy agents likely contributes to SOS, patient heterogeneity and the variety of chemotherapeutic regimens employed in patients in this analysis likely limited the statistical power to interrogate the effects of individual drugs.

Dosimetric uncertainty

One limitation of this report is that all studies used for whole liver modeling applied prescribed doses as surrogates

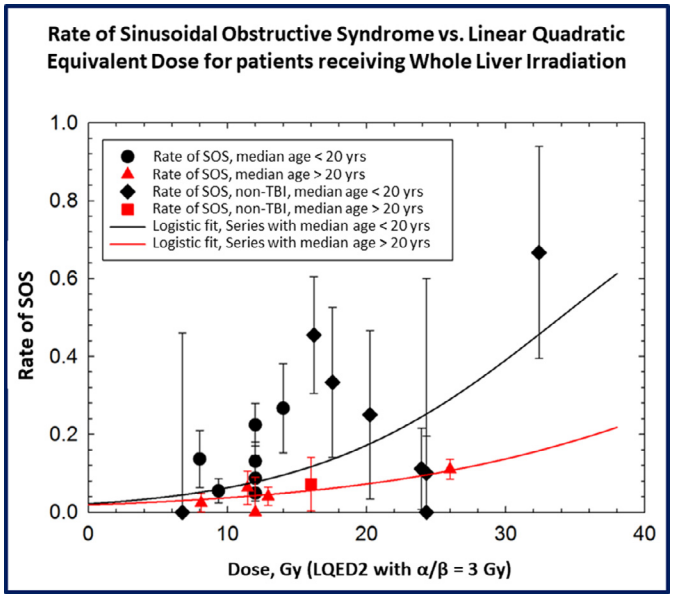

Fig. 2. Rate of sinusoidal obstructive syndrome (SOS) as a function of linear quadratic equivalent dose at 2 Gy per fraction (LQED2) with α/β = 3 Gy in patients receiving whole liver irradiation. Data are stratified by patient age <20 (black) and ≥20 years (red). The solid lines illustrate the logistic regression for each age cohort for the combined total body irradiation (TBI) and non-TBI groups. Note that the median age for all series listed as <20 years of age were in fact <12 years of age.

for whole liver doses. This may introduce random errors or lead to either underestimation or overestimation of whole liver doses owing to liver blocking or boosting, respectively. Uncertainty analysis is described in Appendix E2.

Partial liver results

From 2103 abstracts, 2 articles reported SOS incidence following partial liver RT; both included patients with Wilms tumor treated with left and right flank irradiation. Figure 3 illustrates the dose response plots for SOS as a function of left and right flank irradiation. Qualitatively, patients treated with higher doses and right flank RT had a higher observed rate of hepatic SOS than patients receiving left flank RT, but data were insufficient to generate an NTCP model for partial liver irradiation.

Despite the largely standardized treatment techniques used for flank irradiation in Wilms tumor, limited data exist in the literature on liver dose and dose-volume metrics. To help resolve this data gap and the range of dose-volume exposures associated with complication rates illustrated in

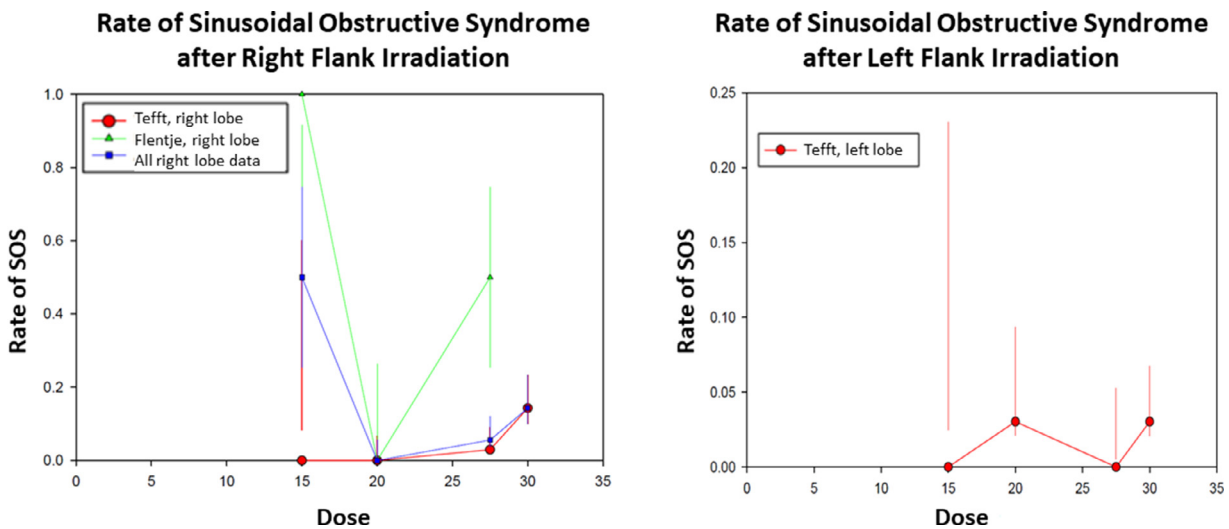

Fig. 3. Dose response plots for sinusoidal obstructive syndrome (SOS) in patients with Wilms tumor treated with left and right flank irradiation from Tefft et al[44] and Flentje et al.[22] Patients treated with higher doses and right flank radiation therapy had higher observed rates of hepatic SOS than patients receiving left flank radiation therapy.

Figure 3, a flank RT simulation study was performed (by R. M.H., S.H., and C.A.O.) to understand the range of liver doses and dose-volume metrics from left and right flank RT.

Flank irradiation simulation study in pediatric and adolescent reference phantoms

Flank RT fields were simulated using pediatric and adolescent computational phantoms, and a sensitivity analysis was performed, adjusting for variable field borders, prescription doses, and patient ages. The objective was to estimate partial volume liver dosimetry data and characterize the spectrum of liver doses that would be delivered during left and right flank RT in patients with Wilms tumor.

Historically, patients with Wilms tumor, including those identified in our search, were treated with parallel-opposed anterior-to-posterior (AP) and posterior-to-anterior (PA) flank fields either directed to the right or left side of the abdomen and pelvis. In our analysis, the base case field borders were defined based on the following anatomic landmarks: (1) superior, T10-T11 vertebral interspace; (2) inferior, L4-L5 vertebral interspace; (3) medial, 1 cm lateral to the vertebral bodies; and (4) lateral, 2 cm beyond the external body contour.

Within a clinically commissioned commercial treatment planning system (RayStation version 11B; RaySearch Laboratories, Stockholm, Sweden), Wilms tumor flank irradiation was simulated on age 1-, 5-, and 10-year-old male and female CT-based phantoms from the International Commission on Radiation Protection (ICRP-143) pediatric/adolescent reference phantom series.[35] For each phantom's CT images, both left and right Wilms 6 MV AP/PA flank RT plans (normalized to midplane) were simulated using the field borders described.

Treatment plans were generated using prescribed doses of 10.8 Gy, 19.8 Gy, 30.6 Gy, and 39.6 Gy, which were selected to conform to modern RT dose prescriptions. We acknowledge that historical treatments led patients to receive doses up to 40 Gy, which are no longer clinically applicable. The superior field border was also modeled at T11-T12 and T9-T10 interspaces to assess changes in liver dosimetry with variation of this field border. The simulated left and right flank fields resulted in dose gradients across the liver, with portions of the liver being in-field and out-of-field. Significantly more liver was in-field for right-sided flank fields and when more cranial superior field borders were used (compared with left-sided fields and more caudal superior field borders). Treatment plan field borders are illustrated in Figure 4. Dose-volume histogram (DVH) data for the 10.8 Gy and 19.8 Gy treatment plans are shown in Figures 5 and 6, respectively; DVH data for the 30.6 Gy and 39.6 Gy treatment plans are shown in Figures 1 and 2 of Appendix E3, respectively. Selected dose and dose-volume metrics (eg, $V_{5\text{-}30}$ and $D_{1\text{-}95}$) for 10.8 Gy, 19.8 Gy, 30.6 Gy, and 39.6 Gy right and left flank RT plans are reported in Tables 1 and 2 of Appendix E3, respectively.

Associating observed partial liver volume complications with the dosimetry metrics from treatments using the most caudal superior border (T11-T12) provides the most conservative assumption from a safety perspective for the rate of reported complications in the literature, because it approximates the minimum volume of liver irradiated that could lead to these complications. Conversely, associating observed partial liver volume complications with the dosimetry metrics from treatments with most cranial superior border (T9-T10) provides the least conservative assumption, because it assumes that a larger volume of irradiated liver would cause the observed complications.

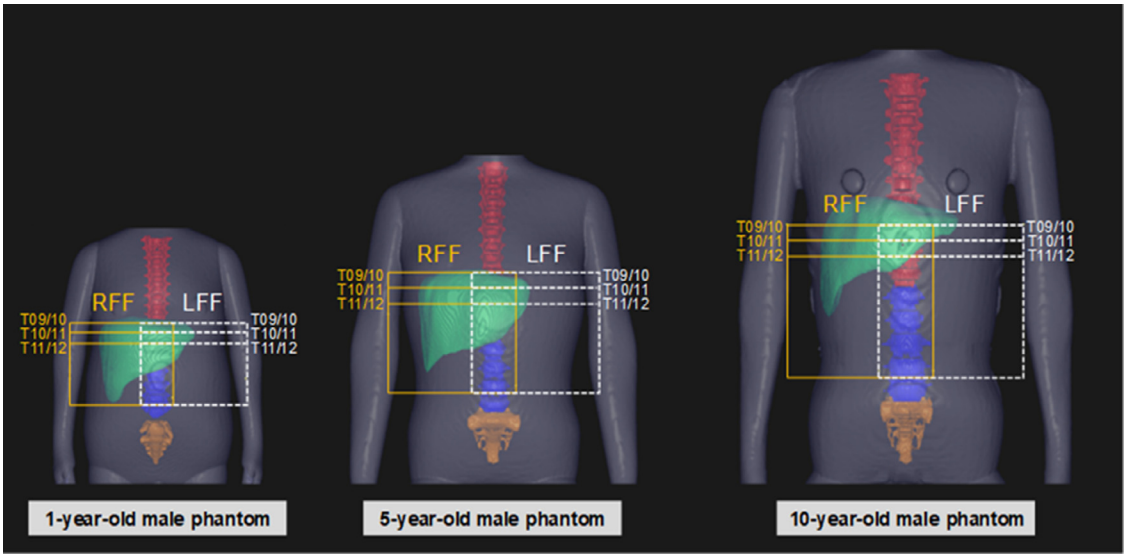

Fig. 4. Illustration of flank field treatment plans simulated on 1-, 5-, and 10-year-old male International Commission on Radiation Protection reference phantoms for simulations with the 3 different superior borders (T9-T10, T10-T11, and T11-T12); right flank field (RFF) and left flank field (LFF) borders are shown in white and yellow, respectively. Liver (green), thoracic spine (red), lumbar spine (blue), and sacrum (brown) are shown.

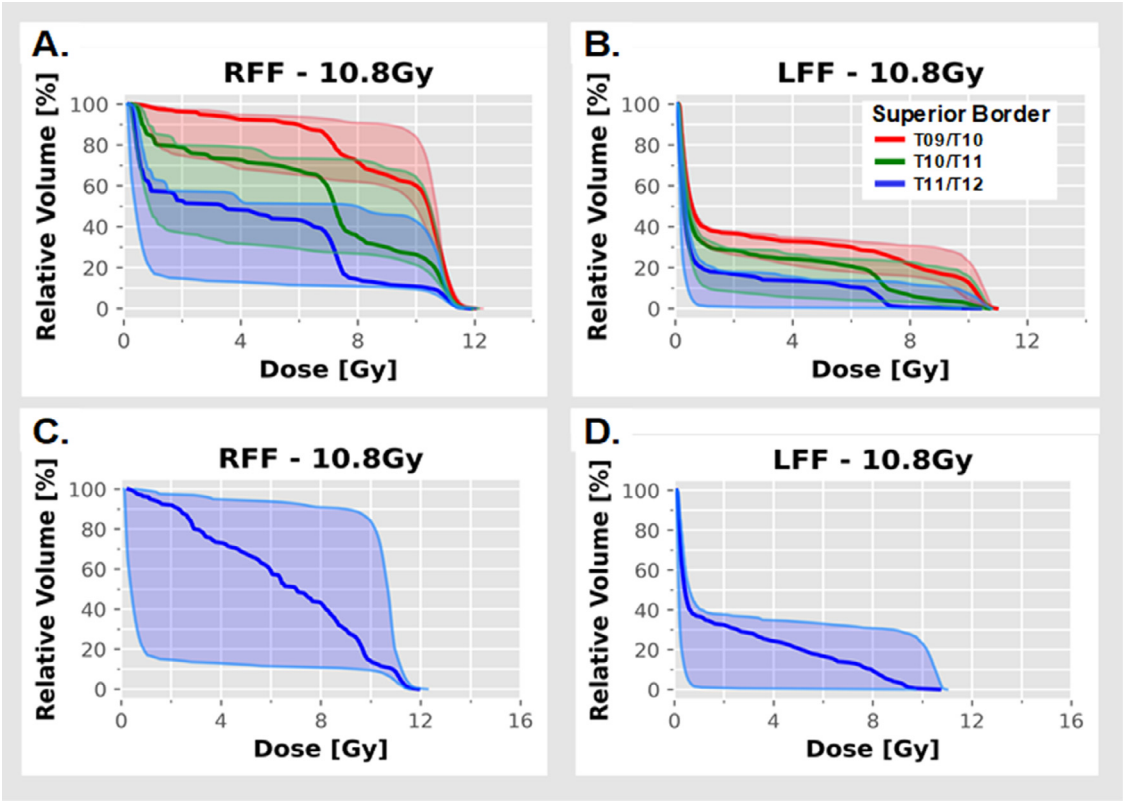

Fig. 5. Dose-volume histogram (DVH) data for the 10.8 Gy flank field treatment plans averaged across the 1-, 5-, and 10-year-old male phantoms for simulations with the 3 different superior borders (T9-T10, T10-T11, and T11-T12); right flank field (RFF) and left flank field (LFF) irradiation are shown in panels A and B, respectively. DVH data averaged across the 3 field borders for RFF and LFF are shown in panels C and D, respectively. Mean DVH data are plotted as solid lines with shaded areas indicating ranges.

Dose, Volume, and Outcome Associations

In QUANTEC, the risk of SOS after whole liver RT to 30 Gy was estimated to be <5%.[1] In this study, the model-predicted SOS rates in children after whole liver doses of 10 Gy and 20 Gy (at 2 Gy per fraction) were 6.1% and 14.5%, respectively. Both RT dose and use of nonalkylating chemotherapy were predictive of SOS after whole liver RT. This suggests that the chemotherapies received by pediatric solid tumor patients and those treated with total body irradiation for HSCT are important risk factors for the development of SOS. In addition, patients <20 years old were more susceptible to SOS than older patients (Figure 2). The model-predicted RT doses (at 2 Gy per fraction) that were associated with a 5% risk of SOS were 8 Gy in patients <20 years old and 14 Gy in patients ≥20 years old. This suggests that pediatric patients are at a higher absolute risk of SOS following whole liver RT than adults receiving the same dose. Some of the observed increased risk may be related to the wider use of concurrent and sequential chemotherapy in children compared with that in adults.

In pediatric patients receiving RT for nonliver target volumes, we recommend using an organ at risk objective of liver mean dose <10 Gy to achieve a risk of SOS of ~6% or less. For patients with liver involvement, mean doses of <20 Gy should be pursued. This is consistent with existing recommendations for patients with Wilms tumor and liver metastases, for whom whole liver irradiation to 19.8 Gy is commonly prescribed. Clinicians should consider the risks and benefits of exceeding these dose limits on a case-by-case basis, as selected patients with tumor involving or near the liver may require higher liver doses to effect cure.

Data were sparse regarding rates of late liver injury, elevated liver enzymes >1 year after treatment, and cirrhosis after exposure to RT. This suggests low rates of chronic liver injury following treatment for common pediatric malignancies.

Risk factors

In this analysis, RT dose, use of nonalkylating chemotherapy, and age were identified as potential risk factors for the development of SOS. Prior studies suggested that the risk of SOS may also be impacted by surgery, HSCT, and selected chemotherapies. A dose response for SOS has been reported in children treated with dactinomycin for Wilms tumor or rhabdomyosarcoma.[34,36,37] In addition, busulfan, methotrexate, mercaptopurine, and thioguanine have also been implicated, but given that most childhood cancer patients

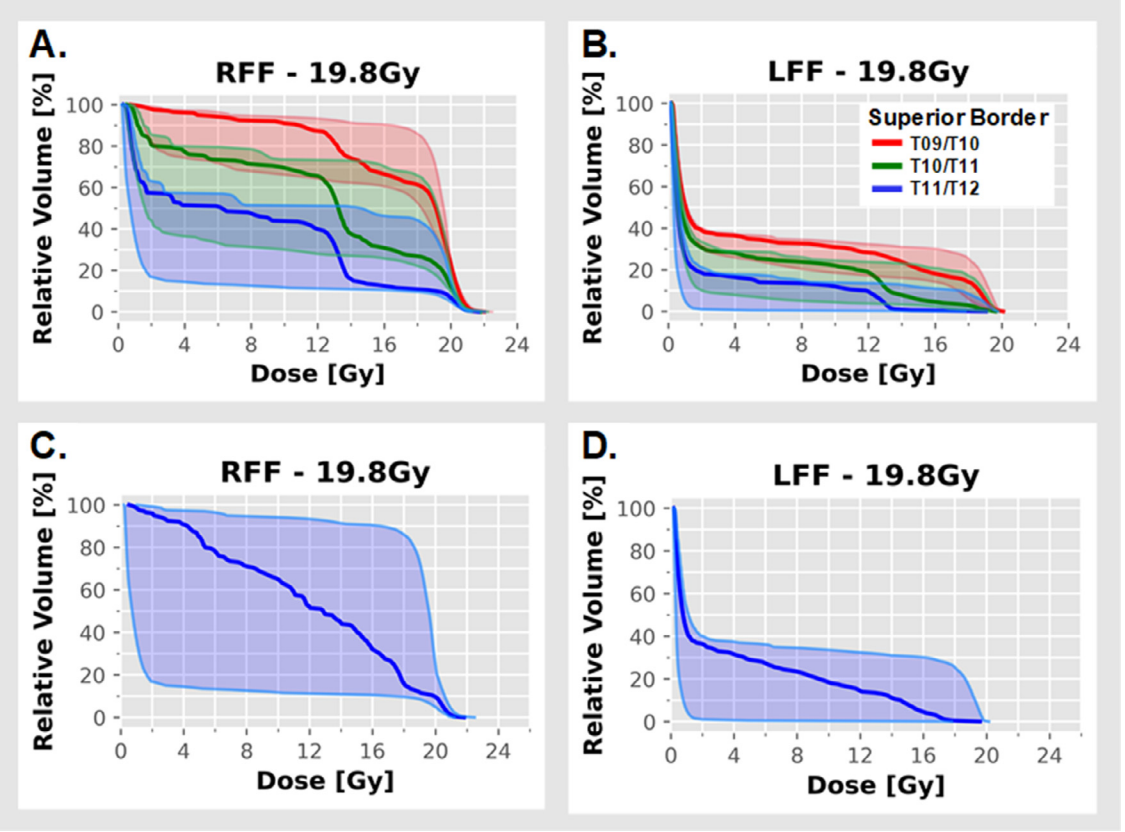

Fig. 6. Dose-volume histogram (DVH) data for the 19.8 Gy flank field treatment plans averaged across the 1-, 5-, and 10-year-old male phantoms for simulations with the 3 different superior borders (T9-T10, T10-T11, and T11-T12); right flank field (RFF) and left flank field (LFF) irradiation are shown in panels A and B, respectively. DVH data averaged across the 3 field borders for RFF and LFF are shown in panels C and D, respectively. Mean DVH data are plotted as solid lines with shaded areas indicating ranges.

receive multiagent chemotherapy, the direct attribution of hepatotoxicity to specific agents is more difficult.

Genetic factors, such as deficiency of thiopurine S-methyltransferase, may also predispose affected patients to SOS owing to skewed antimetabolite processing, resulting in neutropenia and transaminase elevation. The association between variant thiopurine S-methyltransferase genotypes with the more serious sequelae of SOS following thioguanine exposure, however, remain poorly characterized.[38,39] The clinical course of SOS following antimetabolite therapy is generally more indolent than that of cases occurring after HSCT. While most children with thiopurine-associated SOS recover, a subset develop progressive hepatic fibrosis and nodular regenerative hyperplasia,[40,41] which can lead to thrombocytopenia and varying degrees of portal hypertension. SOS following HSCT also differs in its severity and tempo from chemotherapy-associated SOS in the nontransplant setting and is largely attributed to transplant conditioning regimens. A recent genome-wide association study of pediatric patients receiving busulfan found that polymorphisms in the *UGT2B10* and *KIAA1715* genes were noted to confer increased risk of SOS, with some dependence on the conditioning regimen.[42]

Additional predisposing factors for impaired liver health in survivors include history of viral hepatitis, transfusion-related iron overload, exposure to total parenteral nutrition, elevated body mass index, metabolic syndrome, and higher alcohol intake (Figure 7). The prevalence of long-term liver injury in childhood cancer survivors remains poorly characterized, and the associations between acute/subacute toxicity and late liver injury are also unclear.

Limitations

The clinical reports addressing liver toxicities that were identified for this review were scarce. When reported, SOS was by far the most common liver toxicity associated with RT, thereby becoming the focus of this report. The paucity of data in the published literature precludes evaluation of other liver toxicities (eg, hepatic hemorrhage, necrosis, infection, portal hypertension, portal vein thrombosis, focal nodular hyperplasia, cirrhosis, and other late effects).

NTCP modeling was limited by several factors. First, data specific enough to be used in modeling was provided in only 13 articles for whole liver irradiation and 2 articles for

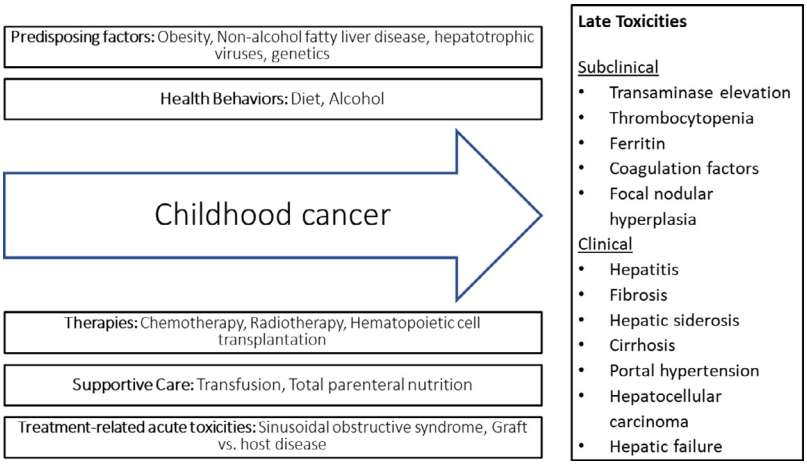

Fig. 7. Multifactorial contributors to liver toxicity in childhood cancer survivors.

partial liver irradiation. As a result, only modeling of SOS following whole liver irradiation was feasible in this report. In many articles, when toxicity and dose-volume exposure of the liver were reported, only the RT dose for the affected patients were included (but not for the unaffected patients). Further, the prescription dose was often reported without specific DVH values received by the liver. When SOS was reported, the incidence could typically be discerned from the articles, but not the severity. Finally, although the data suggest that younger patients, defined herein as age <20 years, are at increased risk of SOS following whole liver irradiation, the data do not permit a more precise estimate for radiosensitivity as a function of age. One can argue that an adolescent liver may be fully developed and may be nearer in maturity to an adult than a child. The age division between adult and pediatric groups in this analysis was largely motivated by the division of these patients between adult and pediatric groups by paper and diagnosis. As a result, the model may underestimate or overestimate the risk of SOS within pediatric patients aged 1 to 20 years.

Toxicity Scoring Recommendations

The following methods for toxicity scoring are recommended:

- Use CTCAE version 5.0 criteria for scoring toxicity for
  - SOS based on laboratory values, imaging, and clinical symptoms
  - Hepatic pain based on clinical evaluation
  - Portal hypertension based on ultrasound imaging and clinical symptoms
  - Hepatic failure based on clinical examination and laboratory values
- Patients with childhood cancer who were treated with abdominal RT or dactinomycin or who developed SOS should enter a long-term follow-up clinic and undergo physical examination and liver function testing, including:
  - Alanine transaminase, aspartate aminotransferase, gamma-glutamyl transferase, total and direct bilirubin, alkaline phosphatase, albumin, and prothrombin time
  - Fasting lipids to evaluate for dyslipidemia
  - Fasting blood glucose or HbA1c to screen for impaired glucose metabolism and diabetes mellitus
  - In addition, all patients with a history of multiple red blood cell transfusions or HSCT should be assessed for iron overload with serum ferritin.
- Patients with abnormal liver enzyme values should undergo repeat testing.
  - If liver enzymes remain abnormal, referral to gastroenterology or hepatology should be considered, particularly if no clear etiology for the elevated enzymes are observed.
- In the event of normal liver enzymes, lipids, and glucose metabolism, subsequent testing should be performed every 1 to 2 years at the discretion of the primary oncology physician(s).
- Patients should be counseled regarding the importance of healthy habits, including vaccination against hepatitis viruses; cautious use or avoidance of alcohol, hepatotoxic drugs (eg, acetaminophen), and supplements; maintenance of healthy body weight and nutrition; and avoidance of obesity, systemic hypertension, and hyperlipidemia.[34,43]

Data Reporting Standards Specific to the Liver

Systematic analyses on liver toxicity following RT are limited by (1) limited or absent dosimetry data provided on RT dose and volume of liver irradiated, (2) small sample sizes in many publications, and (3) pooling of data from patient

cohorts who were treated for variable risk groups and with different RT doses and systemic therapy regimens.

To improve the future understanding of liver toxicity resulting from RT, it is imperative that published data sets provide high-quality, detailed data and adhere to precise reporting standards to facilitate data pooling. Thus, we propose reporting the following information in future studies.

Highest priority for RT-related toxicity reporting

- Patient sex and race
- Cancer diagnosis and stage
- Relevant patient-specific genetic susceptibilities and medical/surgical history (viral hepatitis, cystic fibrosis, Wilson disease, biliary atresia, and history of hepatic surgery)
- Age when treated with RT, attained age at toxicity assessment, and age at last follow-up
- Prescribed RT dose and fractionation
- RT modality and technique (photon: 2-dimensional RT, 3-dimensional conformal RT, intensity-modulated RT; proton therapy: passive scatter, pencil beam scanning, intensity-modulated proton therapy, or dynamic arc; or radiopharmaceutical therapy: I-131 metaiodobenzylguanidine)
- Dosimetry data for all patients both with and without toxicity
  - Liver exposure, described by normal organ DVH with 0.1 Gy dose resolution. When the liver is irradiated, the entire liver should be included in the RT treatment planning scan. The following DVH metrics (at a minimum) should be reported:
    - Mean dose
    - Volume of liver receiving 5, 10, 20, and 30 Gy (eg, $V_{5\text{-}30}$)
- Number of patients included in the study and the number with or without toxicity
  - Toxicity endpoint (yes/no)
  - Description of the toxicity endpoint including how it is measured
  - Description of which toxicity scoring system was used
  - Grade/severity of the toxicity
  - Timing of toxicity onset and resolution

Additional causative factors to be considered in toxicity reporting or assessment

- Chemotherapy (including agents used, number of cycles, and timing with respect to RT)
- HSCT (including conditioning regimen(s) and number of stem cell transplants)
- Chronic graft versus host disease
- Frequency of clinical follow-up for late complications of RT
- Frequency of laboratory and/or imaging follow-up

Future Investigations

Additional studies are needed to better understand the risk of subacute and late liver toxicity in childhood cancer survivors. Future areas of investigation include

- The risk of liver toxicity as a function of DVH relationships, particularly for partial volume RT and SABR
- The risk of liver toxicity following treatment with chemotherapeutic agents (including but not limited to dactinomycin, mercaptopurine, high-dose methotrexate, and busulfan)
- The risk of liver toxicity following liver resection and hematopoietic stem cell transplant
- The risk of liver toxicity associated with novel therapies, including monoclonal antibodies, antibody drug conjugates like gemtuzumab ozogamicin, and inotuzumab ozogamicin, tyrosine kinase inhibitors, and radiopharmaceuticals such as I-131 metaiodobenzylguanidine
- The success of supportive care interventions, currently approved therapies such as defibrotide, and investigational therapies on recovery from SOS-associated liver toxicities
- The risk of late liver toxicity predicted by liver enzyme abnormalities both during SOS and after recovery
- The optimal timing of follow-up evaluations to more accurately collect the incidence of RT-related toxicities and provide surveillance for late effects
- The effect of early medical and lifestyle interventions to improving health in childhood cancer survivors treated with abdominal RT, including maintaining a healthy weight, risk factor modification, and early intervention for hypertension, hyperlipidemia, and glucose intolerance on survival

Single-institution series of pediatric patients are often small, making estimation of the incidence of late effects challenging. Radiation oncologists are strongly advised to commit to collecting DVH and long-term follow-up data on survival and toxicities in pediatric patients with cancer and to consider participating in collaborative database registries to assimilate data across multiple institutions.

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