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Hepato-Biliary Late Effects in Survivors of Childhood and Adolescent Cancer: A Report from the Children's Oncology Group

Sharon Castellino, MD, MS[1,2], **Andrew Muir, MD, MHS**[3], **Ami Shah, MD**[4], **Sheila Shope, FNP**[5,6], **Kevin McMullen, MD**[2,7], **Kathy Ruble, PNP**[8], **Ashley Barber, BA**[2], **Andrew Davidoff, MD**[6,9], and **Melissa M. Hudson, MD**[6,10]

[1] Department of Pediatrics, Winston-Salem, NC

[2] Wake Forest University School of Medicine, Winston-Salem, NC

[3] Department of Medicine, Division of Gastroenterology, Duke University School of Medicine, Durham, NC

[4] Division of BMT, Children's Hospital Los Angeles, Los Angeles, CA

[5] Department of Epidemiology/Cancer Control, St. Jude Children's Research Hospital, Memphis, TN

[6] University of Tennessee Health Science Center, Memphis, TN

[7] Department of Radiation Oncology, Winston-Salem, NC

[8] Department of Pediatrics, Division of Pediatric Oncology, John's Hopkins Hospital

[9] Department of Surgery, St. Jude Children's Research Hospital, Memphis, TN

[10] Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN

Abstract

Curative therapy for childhood and adolescent cancer translates to 1 in 640 young adults being a survivor of cancer. Although acute hepato-biliary toxicity occurs commonly during pediatric cancer therapy, the impact of antineoplastic therapy on long-term liver health in childhood/adolescent cancer survivors is unknown. This article reviews the medical literature on *late* liver dysfunction following treatment for childhood/adolescent cancer. We also outline the Children's Oncology Group (COG) guidelines for screening and follow-up of hepato-biliary sequelae. As the population of survivors grow and age, vigilance for risks to hepatic health needs to continue based on specific exposures during curative cancer therapy.

Keywords

childhood cancer; adolescent cancer survivor; hepato-biliary late effects; screening

Corresponding author: Sharon M Castellino, MD, MS, Wake Forest University, Department of Pediatrics, Hematology/Oncology, Winston-Salem, NC 27157, scastell@wfubmc.edu, Tel: (336)-716-4324, Fax: (336)-716-3010.

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Introduction

With therapeutic advances 80% of children and adolescent cancer patients are expected to become long-term survivors. Current projections are that 1 in 640 adults aged 20–39 years in the US is a childhood cancer survivor.[1] Although antineoplastic therapy is commonly associated with acute and often reversible hepatotoxicity, there is little follow-up on long term liver health in survivors of adult or childhood cancer. Acute or sub-acute hepato-biliary injury is recognized with varying incidence following radiation, multiple chemotherapies, or hematopoietic stem cell transplantation (HSCT).[2,3] Additionally, hepato-biliary toxicity is associated with supportive care measures, such as transfusion-acquired hepatitis, transfusion associated iron overload or cholestatic disease from total parenteral nutrition (TPN). Hepatic dysfunction following graft-versus-host-disease (GVHD), viral hepatitis, or veno-occlusive disease [VOD; also termed sinusoidal obstruction syndrome (SOS)] can also contribute to irreversible hepatic injury.[4] These conditions may predispose to clinically significant liver disease in aging childhood cancer survivors.

This review aims to familiarize clinicians with the *Children's Oncology Group Long*-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers (*COG Guidelines*), focusing on the exposure-based recommendations for screening liver health in survivors.[5]

Methods

In 2003, the COG released risk-based, exposure-related guidelines, to direct follow-up care in patients treated for pediatric malignancies.[5] The *COG Guidelines* represent recommendations for screening asymptomatic survivors for late effects as a result of therapeutic exposures during treatment for pediatric malignancies. The *COG Guidelines* (http://www.survivorshipguidelines.org) were developed to facilitate screening toward early identification of and intervention for cancer-related complications. Outcome specific task forces were organized to refine these initial guidelines through systematic literature reviews and to identify and address gaps in research.

In October 2004 the COG Guideline Task Force on Gastrointestinal and Hepatic Complications performed an extensive review of the English literature, with an update in 2006 and 2008. The search via MEDLINE (National Library of Medicine, Bethesda, MD) encompassed the years 1975–2008. Key search words comprised "childhood cancer therapy," "complications," "late effects" paired with "hepatotoxicity," "hepatic/liver dysfunction," "cholelithiasis," "veno-occlusive disease (VOD)," "hepatoblastoma," "hematopoietic stem cell transplantation (HSCT)," "bone marrow transplantation" and "hepatitis". The search was broadened with references from bibliographies of selected articles.

A multidisciplinary panel of survivorship experts scored the guidelines according to a modified version of the National Comprehensive Cancer Network "Categories of Consensus" system.[6] Scores reflects the panel's assessment of the strength of evidence from the medical literature linking particular adverse outcomes to specific therapeutic exposures, (Table I). High level evidence was defined as evidence derived from randomized control trials, high quality case control or cohort studies with sufficient power to prove the hypothesis. Lower level evidence was defined as that derived from non analytic studies, case reports, case series and clinical experience. For the purpose of the guidelines, evidence scored 1or 2 was then coupled with an assessment of the appropriateness of screening recommendations, based on the expert panel's collective clinical experience.

Results

The task force identified 30 citations from MEDLINE pertaining to non-acute hepatic dysfunction associated with treatment for childhood cancer. These citations included 15 observational studies and 15 non-experimental studies (case reviews and clinical series). Key findings from the literature review are summarized in the sections that follow.

Hepato-Biliary Injury Associated with Cancer Therapy

Acute hepatotoxicity related to antineoplastic therapy has varying pathophysiology including cholestasis, hepatocellular necrosis, ductal injury, steatosis, and veno-occlusion.[7–11] Histological findings include periportal and concentric fibrosis and injury to sinusoidal endothelial cells.[2,3,7] Chronic or delayed liver injury following childhood cancer is from hepatic fibrosis in response to inflammation from chronic viral hepatitis, drug-induced injury or fatty infiltration. Progressive fibrosis leads to risk for cirrhosis, portal hypertension and hepatocellular carcinoma.[12–14] Chronic GVHD involving the liver after HSCT is associated with hepatocellular necroinflammatory changes, paucity of interlobular bile ducts, and intrahepatic cholestasis.[15]

Clinical Manifestations of Late Hepato-Biliary Toxicity

Liver injury related to treatment for childhood cancer can be indolent and develop without a history of prior acute toxicity; however data is not available correlating the incidence of chronic liver disease to acute hepatotoxicity. Asymptomatic elevations of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are nonspecific indicators of acute injury during therapy, and hence nonspecific to delayed injury in survivors. With chronic GVHD, serum alkaline phosphatase and bilirubin levels may also be elevated.

In contrast to the acute presentation of hepatic VOD/SOS, late sequelae are characterized by painless hepatomegaly, esophageal or gastric varices, or splenomegaly with thrombocytopenia. [12,16] If decompensated cirrhosis develops, constitutional complaints and clinical signs and symptoms are similar to that in the general population.

Late Hepatic Sequelae of Chemotherapy

In contrast to the knowledge about acute and sub acute hepatic effects, limited data are available regarding chronic persistent or latent hepatic dysfunction from chemotherapy administered in childhood. The latency period for manifestation of liver dysfunction is unknown and therefore challenging to establish links between hepato-biliary events in adulthood and prior cancer history. The agents with established acute and emerging chronic hepatotoxic potential include antimetabolite agents like 6-mercaptopurine, 6-thioguanine, methotrexate, and rarely dactinomycin (Table II).

Thiopurines—The antimetabolites, 6-thioguanine and 6-mercaptopurine have established associations with subacute hepatocellular and cholestatic disease.[2] One underlying genetic risk for acute toxicity in patients is thiopurine S-methyltransferase (TPMT) deficiency. The rare, but severe acute toxicity of these antimetabolites, and 6-thiguanine specifically is the occurrence of VOD/SOS.[16,17] Although the majority of children with this complication of thiopurine associated VOD recover, a subset of patients have progressive fibrosis leading to portal hypertension.[12,16,18] Late liver dysfunction manifests as persistent hepatomegaly, splenomegaly, and thrombocytopenia.[12,19] Chronic viral hepatitis, TPMT homozygosity and hemosiderosis are proposed contributors to chronic fibrosis in these survivors.

Methotrexate—Acute and subacute methotrexate-induced hepatic injury is characterized by transient elevations of serum transaminases or alkaline phosphatase; biochemical changes

do not consistently correlate with severity of hepatic injury.[19] The risk of fibrosis or cirrhosis after daily oral methotrexate is more than two-fold greater than intermittent parenteral administration in some childhood leukemia treatment protocols.[20] More contemporary studies evaluating hepatic histology in children treated with methotrexate demonstrated mild structural changes and low incidence of portal fibrosis.[19,21] These findings suggest that methotrexate-induced fibrosis regresses or stabilizes after discontinuation and rarely produces end-stage liver disease in the absence of other antimetabolite therapy, or co-morbidities.[19] Interestingly there have been no reports of delayed hepatotoxicity in osteosarcoma survivors who receive shorter duration, high dose methotrexate despite elevated transaminases levels during therapy.

Notably, in survivors of leukemia with viral hepatitis who received high dose, parenteral or oral methotrexate regimens, there is growing evidence that the risk for progressive hepatic dysfunction persists into adulthood.[13,22] Hepatic radiation may contribute added risk for progression of late methotrexate hepatic sequelae.

Dactinomycin—Dactinomycin is associated with acute, dose related, reversible VOD/SOS in children treated for Wilms tumor and rhabdomyosarcoma.[23,24] Despite the acute hepatic dysfunction in the non-irradiated patients, overall survival exceeded 80% in the National Wilms Tumor Study. The prevalence of chronic hepatopathy with follow-up is unknown.

Hepatic Sequelae after Radiation

Radiation induced liver disease (RILD) typically presents in the first 12 weeks after completion of radiation and resembles VOD/SOS resulting from endothelial cell injury.[25] Pediatric hepatic radiation dose limits have not been characterized, but in adults, where the whole liver has tolerance up to 30–35 Gy with conventional fractionation, the prevalence of radiation liver disease varies from 6–66% based on the volume of liver involved and on hepatic reserve.[25,26] Smaller volumes of liver may be safely irradiated to higher doses, while accounting for the radio-sensitizing effects of chemotherapy. RILD has been studied in children with Wilms tumor, neuroblastoma, and hepatoblastoma.[27–30] The risk of injury increases with radiation dose, hepatic volume, younger age at treatment, prior partial hepatectomy, and concomitant use of radiomimetic chemotherapy like dactinomycin and doxorubicin.[27,29]

Persistent radiation hepatopathy after contemporary treatment is uncommon in long term survivors without predisposing conditions, such as viral hepatitis or iron overload.[31] Survivors who received radiation doses of ≥ 40 Gy to at least one third of liver volume, doses of ≥ 30 Gy to whole abdomen, or an upper abdominal field involving the entire liver are at highest risk for hepatic dysfunction. The evidence for a clear association of secondary hepatic malignancies within the radiation field is limited. [32–34] Contemporary three-dimensional planning permits more accurate delivery of high-dose radiation to tumors while sparing normal liver. Long-term outcome of liver function following contemporary technology are not yet available.

Hepatic Sequelae of HSCT

Liver disease in long-term survivors treated with HSCT in childhood may result from chronic GVHD, chronic viral infection, VOD/SOS, or nodular regenerative hyperplasia. [35,36] Chronic GVHD is the leading cause of non-relapse mortality 2 years post HSCT, and approximately 80% of individuals with chronic GVHD have liver involvement.[37] Chronic GVHD manifests as cholestasis with elevated bilirubin and alkaline phosphatase, but may also present as acute hepatitis alone. Immunosuppressive agents, antibiotics,

antifungal and antiviral drugs, sedatives, anti-emetics, antipyretics, and parenteral nutrition may exacerbate chronic GVHD associated hepatotoxicity.[15]

Liver dysfunction with cirrhosis due to chronic viral hepatitis represents an important late complication of HSCT.[4,36,38] Chronic liver disease may predispose to early mortality in long-term survivors after HSCT.[4,38,39]

The risk of developing VOD/SOS ranges from 1 to 54% with HSCT with high mortality rates.[40] Cyclophosphamide and busulfan conditioning and total body irradiation regimens are associated with the highest incidence of fatal VOD. Due to the high mortality rate of VOD/SOS, there are no studies evaluating long term hepato-biliary health in HSCT survivors of this condition.

Siderosis is found in approximately 90% of long term survivors of HSCT.[41] Iron overload results from multiple red cell transfusions and dyserythropoiesis leading to increased iron transport through the intestine. Iron overload may exacerbate the course of viral hepatitis.

Transfusion-Acquired Hepatitis

Infectious hepatitis has been a major contributor to liver morbidity and mortality following childhood cancer, especially in survivors transfused prior to effective screening measures for hepatitis B (HBV) and C (HCV).[13,36,42,43] Based on the implementation of effective screening of blood products in the U.S., survivors at highest risk are those exposed to blood/serum products prior to 1972 for HBV and prior to 1993 for HCV (Table III).

HBV is characterized by a more aggressive acute clinical course and a lower rate of chronic infection. In contrast, acute infection with HCV is often mild or asymptomatic, but the rate of chronic infection approximates 80%.[44] Survivors with chronic hepatitis may experience significant morbidity and mortality related to cirrhosis and hepatocellular carcinoma.[43]

The prevalence of transfusion related HCV infection (positive EIA or PCR) has ranged from 5% to 50% depending on the geographic location of the cancer center.[13,42,43,45–47] Chronic infection is common, evidenced by PCR detection of viral RNA ranging from 70% to 100%.[13,45–47] Most patients are asymptomatic, with elevated ALT values in 29% to 79%. Chronically infected survivors develop progressive fibrosis and cirrhosis at rates similar to adult HCV cohorts, or hemophiliacs co-infected with human immunodeficiency virus (HIV) and HBV.[13] Co-infection with HBV and HCV might accelerate disease progression as does concomitant immunosuppression or HSCT associated hepatotoxicity.[14,43] Hepatocellular carcinoma is largely associated with chronic HBV and HCV infection.[14,48]

Other Late Hepato-Biliary Complications

Less commonly reported hepato-biliary complications include cholelithiasis, focal nodular hyperplasia (FNH), nodular regenerative hyperplasia (NRH), and microvesicular fatty change. In a large cohort of childhood patients with cancer, Mahmoud et al. reported a higher risk of biliary calculi in compared to rates observed in the general population.[49] The cumulative risk of cholelithiasis was 0.42% at 10 years and 1.03% at 18 years after diagnosis. Treatment factors associated with cholelithiasis included: ileal conduit (RR 61.6; 27.9–135.9), parenteral nutrition (RR 23.0; 9.8–54.1), abdominal surgery (RR 15.1; 7.1–32.2), and abdominal radiation (RR 7.4; 3.2–17.0). HSCT has also has been associated with cholelithiasis. [50]

FNH is often an incidental finding on imaging in childhood cancer survivors, with no specific therapeutic association. [51–54] The pathogenesis of FNH albeit poorly understood,

is thought to be a reaction to a localized vascular anomaly. Others have speculated that FNH results from thrombosis, intimal hyperplasia, high sinusoidal pressures, or increased flow.[53,55] High doses of alkylating agents, history of VOD/SOS, or hepatic radiation may produce vascular injury and subsequent localized circulatory disturbances.[52] The FNH lesion is characterized with specificity by MRI, and is associated with infrequent complications and the absence of malignant transformation.

NRH is a rare condition characterized by the development of multiple monoacinar regenerative hepatic nodules and mild fibrosis. The pathogenesis is not well established, but may represent a non-specific tissue adaptation to heterogeneous hepatic blood flow.[56] NRH has rarely been observed in survivors of childhood cancer treated with chemotherapy, with or without liver radiotherapy.[18,51,57] Biopsy may be necessary to distinguish NRH from a second malignancy.

In a cohort who recently completed intensified therapy for acute lymphoblastic leukemia, histological evidence of fatty infiltration was noted in 93% and siderosis in up to 70% of patients.[58] Fibrosis developed in 11% and was associated with higher serum LDL-cholesterol. Prospective studies are needed to define whether acute post-therapy fatty liver change contributes to the development of steatohepatitis or the metabolic syndrome in this population.

Discussion

The growing population of childhood cancer survivors will transition from pediatric oncology to primary medical care at varying intervals after completing therapy. For each potential late treatment complication, the *COG Guidelines* outline host co-morbidities, treatment factors and health behaviors that may heighten the risk for toxicity in association with the predisposing antineoplastic therapy. Because the literature addressing the risks and benefits of screening asymptomatic childhood cancer survivors is limited, the current guidelines provide conservative screening recommendations derived from the consensus of a multi-disciplinary panel of late effects experts. Thus, the guidelines address the Institute of Medicine's call to develop health screening recommendations appropriate to the unique vulnerabilities of childhood cancer survivors.[1]

With regard to survivors exposed to potentially hepatotoxic therapy in childhood, the recommendations are for screening evaluation of ALT, AST, and bilirubin at baseline entry into long-term follow-up. Serum ferritin is an additional recommendation at baseline for survivors of HSCT (Table II). Childhood cancer exposures may be an emerging contributor to the 3 to 5% of the population with asymptomatic persistent non-virus non-alcohol related aminotransferase elevation.[59] The COG guidelines provide recommendation for additional evaluation in the setting of positive screening for those who received antimetabolites, abdominal irradiation or HSCT. Since a high proportion of at-risk survivors and their non-oncology providers are unaware of transfusion exposure status,[60] the *COG Guidelines* recommend that *all* patients treated prior to 1972 should have screening for hepatitis B and all patients treated prior to 1993 should have screening with a serum hepatitis C antibody test. These dates will vary for patients who received transfusions at non-U.S. institutions. Further testing for the hepatitis C virus should be given to antibody negative patients with abnormal serum transaminases, hyperbilirubinemia, or those who may have a false negative antibody test because of persistent immunosuppression (Table III). Testing for viral hepatitis is warranted as effective antiviral regimens are increasingly available.

Health literacy to minimize further hepatic injury is important toward health maintenance in childhood cancer survivors with a history of exposure to hepatotoxic therapy. Health

education toward this goal include avoidance of obesity, viral hepatitis risk prevention, and careful attention of health providers to survivors' prescription and non-prescription drug use, and herbal and supplement use (http://www.hepfi.org/living/liv_caring.html).[61–64] Standard behavioral recommendations include abstinence from alcohol use and immunization against hepatitis A and B if immunity is not established. Although studies specifically evaluating recommendations to promote liver health in childhood cancer survivors have not been conducted, a conservative approach adopting recommendations from other specialties modified for survivors is appropriate. Practitioners can access patient materials on liver health by visiting the "Health Links" at http://www.survivorshipguidelines.org/.

In conclusion, delayed hepato-biliary sequelae are currently reported with low incidence, despite the frequency of acute hepatotoxicity observed during childhood cancer treatment. Survivors of leukemia and HSCT have the highest rates of risk for late hepatic dysfunction. As liver disease can be indolent, risk-based health screening and proactive intervention against long-term adverse effects provide an opportunity to reduce cancer related morbidity and improve quality of life in the growing population of adults surviving childhood cancer. The unknown interaction between therapies delivered during childhood with health behaviors and co-morbidities of usual aging need to be considered in continued follow-up of this population. Given the sparse literature on late hepatobiliary effects, further research is needed to identify the true incidence and the ensuing natural history of latent liver dysfunction in childhood cancer survivors of contemporary therapy, including those who have sustained large liver resection or liver transplant for childhood cancers.

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References

1. Hewitt, M.; Weiner, S.; Simone, J., editors. Childhood cancer survivorship:improving care and quality of life. Washington, DC: National Academies Press; 2003.
2. Floyd J, Mirza I, Sachs B, et al. Hepatotoxicity of chemotherapy. Semin Oncol. 2006; 33(1):50–67. [PubMed: 16473644]
3. Rodriguez-Frias EA, Lee WM. Cancer chemotherapy II: atypical hepatic injuries. Clin Liver Dis. 2007; 11(3):663–676. viii. [PubMed: 17723925]
4. Socie G, Stone JV, Wingard JR, et al. Long-term survival and late deaths after allogeneic bone marrow transplantation. Late Effects Working Committee of the International Bone Marrow Transplant Registry. N Engl J Med. 1999; 341(1):14–21. [PubMed: 10387937]
5. Landier W, Bhatia S, Eshelman DA, et al. Development of risk-based guidelines for pediatric cancer survivors: the Children's Oncology Group Long-Term Follow-Up Guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline. J Clin Oncol. 2004; 22(24):4979–4990. [PubMed: 15576413]
6. Winn RJ, Botnick WZ. The NCCN Guideline Program: a conceptual framework. Oncology (Williston Park). 1997; 11(11A):25–32. [PubMed: 9430176]
7. Patrick, RS.; McGee, JOD. Biopsy pathology of the liver. London: Chapman Hall, Ltd; 1980.
8. McDonald GB, Tirumali N. Intestinal and liver toxicity of antineoplastic drugs. West J Med. 1984; 140(2):250–259. [PubMed: 6375139]
9. McDonald GB, Sharma P, Matthews DE, et al. Venocclusive disease of the liver after bone marrow transplantation: diagnosis, incidence, and predisposing factors. Hepatology. 1984; 4(1):116–122. [PubMed: 6363247]

10. Perry M. Chemotherapeutic agents and hepatotoxicity. Semin Oncol. 1992; 19(5):551–565. [PubMed: 1411653]
11. Miano M, Faraci M, Dini G, et al. Early complications following haematopoietic SCT in children. Bone Marrow Transplant. 2008; 41 (Suppl 2):S39–42. [PubMed: 18545243]
12. Broxson EH, Dole M, Wong R, et al. Portal hypertension develops in a subset of children with standard risk acute lymphoblastic leukemia treated with oral 6-thioguanine during maintenance therapy. Pediatr Blood Cancer. 2005; 44(3):226–231. [PubMed: 15503293]
13. Castellino S, Lensing S, Riely C, et al. The epidemiology of chronic hepatitis C infection in survivors of childhood cancer: an update of the St Jude Children's Research Hospital hepatitis C seropositive cohort. Blood. 2004; 103(7):2460–2466. [PubMed: 14684419]
14. Strickland DK, Jenkins JJ, Hudson MM. Hepatitis C infection and hepatocellular carcinoma after treatment of childhood cancer. J Pediatr Hematol Oncol. 2001; 23(8):527–529. [PubMed: 11878782]
15. Shulman, H. Pathology of chronic graft-vs.-host disease. In: Burakoff, S., editor. Graft-vs-Host Disease Immunology, Pathophysiology and Treatment. New York: Marcel Dekker; 1990.
16. Piel B, Vaidya S, Lancaster D, et al. Chronic hepatotoxicity following 6-thioguanine therapy for childhood acute lymphoblastic leukaemia. Br J Haematol. 2004; 125(3):410–411. author reply 412. [PubMed: 15086428]
17. Lennard L, Richards S, Cartwright CS, et al. The thiopurine methyltransferase genetic polymorphism is associated with thioguanine-related veno-occlusive disease of the liver in children with acute lymphoblastic leukemia. Clin Pharmacol Ther. 2006; 80(4):375–383. [PubMed: 17015055]
18. De Bruyne R, Portmann B, Samyn M, et al. Chronic liver disease related to 6-thioguanine in children with acute lymphoblastic leukaemia. J Hepatol. 2006; 44(2):407–410. Epub 2005 Jul 2018. [PubMed: 16226335]
19. Parker D, Bate CM, Craft AW, et al. Liver damage in children with acute leukaemia and non-Hodgkin's lymphoma on oral maintenance chemotherapy. Cancer Chemother Pharmacol. 1980; 4(2):121–127. [PubMed: 6930333]
20. Hutter RVPSF, Tan CTC, Murphy ML, Chowdhury M. Hepatic fibrosis in children with acute leukemia: a complication of therapy. Cancer. 1960; 13:288–307. [PubMed: 14405648]
21. Halonen P, Mattila J, Makipernaa A, et al. Erythrocyte concentrations of metabolites or cumulative doses of 6-mercaptopurine and methotrexate do not predict liver changes in children treated for acute lymphoblastic leukemia. Pediatr Blood Cancer. 2006; 46(7):762–766. [PubMed: 16395677]
22. Farrow AC, Buchanan GR, Zwiener RJ, et al. Serum aminotransferase elevation during and following treatment of childhood acute lymphoblastic leukemia. J Clin Oncol. 1997; 15(4):1560–1566. [PubMed: 9193353]
23. Green DM, Norkool P, Breslow NE, et al. Severe hepatic toxicity after treatment with vincristine and dactinomycin using single-dose or divided-dose schedules: a report from the National Wilms Tumor Study. J Clin Oncol. 1990; 8(9):1525–1530. [PubMed: 2167951]
24. Sulis ML, Bessmertny O, Granowetter L, et al. Veno-occlusive disease in pediatric patients receiving actinomycin D and vincristine only for the treatment of rhabdomyosarcoma. J Pediatr Hematol Oncol. 2004; 26(12):843–846. [PubMed: 15591910]
25. Dawson LA, Haken RKT. Partial Volume Tolerance of the Liver to Radiation. Semin Radiat Oncol. 2005; 15:279–283. [PubMed: 16183482]
26. Milano MT, Constine LS, Okunieff P. Normal Tissue Tolerance Dose Metrics for Radiation Therapy of Major Organs. Semin Radiat Oncol. 2007; 17:131–140. [PubMed: 17395043]
27. Bhanot P, Cushing B, Philippart A, et al. Hepatic irradiation and adriamycin cardiotoxicity. J Pediatr. 1979; 95(4):561–563. [PubMed: 225461]
28. Flentje M, Weirich A, Potter R, et al. Hepatotoxicity in irradiated nephroblastoma patients during postoperative treatment according to SIOP9/GPOH. Radiother Oncol. 1994; 31(3):222–228. [PubMed: 8066205]
29. Kun LE, Camitta BM. Hepatopathy following irradiation and adriamycin. Cancer. 1978; 42(1):81–84. [PubMed: 667811]

30. Tefft M. Radiation related toxicities in National Wilms Tumor Study Number 1. Int J Radiat Oncol Biol Phys. 1977; 2(5–6):455–463. [PubMed: 195920]
31. Barnard JAMG, Neblett WW, Gray G, Ghishan FK. Noncirrhotic portal fibrosis after Wilms tumor therapy. Gastroenterology. 1986; 90:1054–1056. [PubMed: 3005103]
32. Blatt J, Olshan A, Gula MJ, et al. Second malignancies in very-long-term survivors of childhood cancer. Am J Med. 1992; 93(1):57–60. [PubMed: 1320804]
33. Greten TF, Manns MP, Reinisch I, et al. Hepatocellular carcinoma occurring after successful treatment of childhood cancer with high dose chemotherapy and radiation. Gut. 2005; 54(5):732. [PubMed: 15831932]
34. Bassal M, Mertens AC, Taylor L, et al. Risk of selected subsequent carcinomas in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Clin Oncol. 2006; 24(3): 476–483. [PubMed: 16421424]
35. Socie G, Salooja N, Cohen A, et al. Nonmalignant late effects after allogeneic stem cell transplantation. Blood. 2003; 102(7):2695. [PubMed: 14504068]
36. Locasciulli A, Testa M, Valsecchi MG, et al. Morbidity and mortality due to liver disease in children undergoing allogeneic bone marrow transplantation: a 10-year prospective study. Blood. 1997; 90(9):3799–3805. [PubMed: 9345068]
37. Fisher VL. Long-term follow-up in hematopoietic stem-cell transplant patients. Pediatr Transplant. 1999; 3 (Suppl 1):122–129. [PubMed: 10587982]
38. Yau JC, Zander AR, Srigley JR, et al. Chronic graft-versus-host disease complicated by micronodular cirrhosis and esophageal varices. Transplantation. 1986; 41(1):129–130. [PubMed: 3510486]
39. Knapp ABCJ, Rappeport JM, Gollan JL. Cirrhosis as a consequence of graft versus hostdisease. Gastroenterology. 1987; 92(2):513–519. [PubMed: 3539693]
40. Bearman SI. The syndrome of hepatic veno-occlusive disease after marrow transplantation. Blood. 1995; 85(11):3005–3020. [PubMed: 7756636]
41. McKay PJ, Murphy JA, Cameron S, et al. Iron overload and liver dysfunction after allogeneic or autologous bone marrow transplantation. Bone Marrow Transplant. 1996; 17(1):63–66. [PubMed: 8673057]
42. Locasciulli A, Testa M, Pontisso P, et al. Prevalence and natural history of hepatitis C infection in patients cured of childhood leukemia. Blood. 1997; 90(11):4628–4633. [PubMed: 9373275]
43. Paul IM, Sanders J, Ruggiero F, et al. Chronic hepatitis C virus infections in leukemia survivors: prevalence, viral load, and severity of liver disease. Blood. 1999; 93(11):3672–3677. [PubMed: 10339473]
44. Recommendations for prevention and control of hepatitis C virus (HCV) and HCV-related disease. Atlanta, GA: Centers for Disease Control and Prevention; 1998 October 16. p. 1-39.1998. Report nr 47 (RR-19)
45. Arico M, Maggiore G, Silini E, et al. Hepatitis C virus infection in children treated for acute lymphoblastic leukemia. Blood. 1994; 84(9):2919–2922. [PubMed: 7949165]
46. Cesaro S, Petris MG, Rossetti F, et al. Chronic hepatitis C virus infection after treatment for pediatric malignancy. Blood. 1997; 90(3):1315–1320. [PubMed: 9242567]
47. Fink FM, Hocker-Schulz S, Mor W, et al. Association of hepatitis C virus infection with chronic liver disease in paediatric cancer patients. Eur J Pediatr. 1993; 152(6):490–492. [PubMed: 7687544]
48. Fujisawa T, Komatsu H, Inui A, et al. Long-term outcome of chronic hepatitis B in adolescents or young adults in follow-up from childhood. J Pediatr Gastroenterol Nutr. 2000; 30(2):201–206. [PubMed: 10697141]
49. Mahmoud H, Schell M, Pui CH. Cholelithiasis after treatment for childhood cancer. Cancer. 1991; 67(5):1439–1442. [PubMed: 1899356]
50. Safford SD, Safford KM, Martin P, et al. Management of cholelithiasis in pediatric patients who undergo bone marrow transplantation. J Pediatr Surg. 2001; 36(1):86–90. [PubMed: 11150443]
51. Chu WC, Roebuck DJ. Nodular regenerative hyperplasia of the liver simulating metastases following treatment for bilateral Wilms tumor. Med Pediatr Oncol. 2003; 41(1):85–87. [PubMed: 12764757]

52. Bouyn CI, Leclere J, Raimondo G, et al. Hepatic focal nodular hyperplasia in children previously treated for a solid tumor. Incidence, risk factors, and outcome. Cancer. 2003; 97(12):3107–3113. [PubMed: 12784348]
53. Kumagai H, Masuda T, Oikawa H, et al. Focal nodular hyperplasia of the liver: direct evidence of circulatory disturbances. J Gastroenterol Hepatol. 2000; 15(11):1344–1347. [PubMed: 11129233]
54. Stocker JT, Ishak KG. Focal nodular hyperplasia of the liver: a study of 21 pediatric cases. Cancer. 1981; 48(2):336–345. [PubMed: 7237404]
55. Wanless IR, Lentz JS. Fatty liver hepatitis (steatohepatitis) and obesity: an autopsy study with analysis of risk factors. Hepatology. 1990; 12(5):1106–1110. [PubMed: 2227807]
56. Wanless IR. Micronodular transformation (nodular regenerative hyperplasia) of the liver: a report of 64 cases among 2,500 autopsies and a new classification of benign hepatocellular nodules. Hepatology. 1990; 11(5):787–797. [PubMed: 2189821]
57. Brisse H, Servois V, Bouche B, et al. Hepatic regenerating nodules: a mimic of recurrent cancer in children. Pediatr Radiol. 2000; 30(6):386–393. [PubMed: 10876822]
58. Halonen P, Mattila J, Ruuska T, et al. Liver histology after current intensified therapy for childhood acute lymphoblastic leukemia: microvesicular fatty change and siderosis are the main findings. Med Pediatr Oncol. 2003; 40(3):148–154. [PubMed: 12518342]
59. Morisco F, Pagliaro L, Caporaso N, et al. Consensus recommendations for managing asymptomatic persistent non-virus non-alcohol related elevation of aminotransferase levels: suggestions for diagnostic procedures and monitoring. Dig Liver Dis. 2008; 40(7):585–598. [PubMed: 18395501]
60. Lansdale, M.; Marina, N.; Castellino, S., et al. Screening for Hepatitis C virus (HCV) Infection in Long-term Pediatric Cancer Survivors: A Report from the Childhood Cancer Survivor Study (CCSS). Bethesda, MD: 2006. Report
61. Bellizzi KM, Rowland JH, Jeffery DD, et al. Health behaviors of cancer survivors: examining opportunities for cancer control intervention. J Clin Oncol. 2005; 23(34):8884–8893. [PubMed: 16314649]
62. Becker U, Deis A, Sorensen TI, et al. Prediction of risk of liver disease by alcohol intake, sex, and age: a prospective population study. Hepatology. 1996; 23(5):1025–1029. [PubMed: 8621128]
63. Chitturi S, George J. Hepatotoxicity of commonly used drugs: nonsteroidal anti-inflammatory drugs, antihypertensives, antidiabetic agents, anticonvulsants, lipid-lowering agents, psychotropic drugs. Semin Liver Dis. 2002; 22(2):169–183. [PubMed: 12016548]
64. Estes JD, Stolpman D, Olyaei A, et al. High prevalence of potentially hepatotoxic herbal supplement use in patients with fulminant hepatic failure. Arch Surg. 2003; 138(8):852–858. [PubMed: 12912743]

Table I

Consensus scoring categories for screening and risk based recommendations in the COG Long-term follow-up guidelines

Score	Consensus statement
1	There is uniform consensus of the panel that there is high level evidence linking the late effect with the therapeutic exposure; screening recommendation is appropriate based on collective clinical experience of panel members
2A	There is uniform consensus of the panel that there is lower level evidence linking the late effect with the therapeutic exposure; screening recommendation is appropriate based on collective clinical experience of panel members
2B	There is non uniform consensus of the panel that there is lower-level evidence linking the late effect with the therapeutic exposure; screening recommendation is appropriate based on collective clinical experience of panel members
3	There is major disagreement that the recommendation is appropriate

COG: Children's Oncology Group.

Table II

Cancer therapy associations linked to potential hepato-biliary late effects in survivors of childhood and adolescent cancers

Cancer Treatment Risk factor	Potential Late Effect	Additional Risk Factors	Recommended Evaluation	Evidence Score*
Mercaptopurine Thioguanine	Veno-occlusive disease (VOD)	• Viral hepatitis • Prior VOD • Siderosis		2A
			Screening	
Mercaptopurine Thioguanine Methotrexate	Hepatic dysfunction	• Viral hepatitis • Treatment before 1970 • Abdominal radiation • Prior VOD	• ALT • AST • Bilirubin	
Abdominal radiation ≥ 30 Gy	Hepatic fibrosis Cirrhosis	• Chronic hepatitis	Considerations for additional testing/intervention	
Hematopoietic stem cell transplant (HSCT)	Hepatic dysfunction Chronic hepatitis Cirrhosis Iron overload	• Prior history of VOD • Higher radiation dose (≥ 40 Gy to at • least 1/3 of liver; 20–30 Gy to entire liver) • Alcohol use	• Prothrombin Time • Screen for viral hepatitis • ** Ferritin/measure of liver iron burden • Hepatitis A and B immunizations	
Abdominal Radiation	Cholelithiasis	• Chronic GVHD • Chronic hepatitis • Siderosis • Steatosis • Multiple transfusions • Radiation to liver • Prior antimetabolite therapy • Alcohol use • Obesity	COG Health Links http://www.survivorshipguidelines.org/pdf/LiverHealth.pdf	1 1 2B

Cancer Treatment Risk factor	Potential Late Effect	Additional Risk Factors	Recommended Evaluation	Evidence Score*
		• Pregnancy • Family history of cholelithiasis • Ileal conduit • Abdominal radiation • Abdominal surgery • Total parenteral nutrition (TPN)		

* Screening recommendations and literature evidence for therapy associations can be found at (http://www.survivorshipguidelines.org); GVHD Graft versus host disease;

** Specific to HSCT Survivors

Table III

Monitoring liver health for transfusion-associated morbidity following cancer therapy for childhood and adolescent cancers

Cancer Treatment Period	Potential Late Effect	Additional Risk Factors	Recommended Screening	Evidence Score
Diagnosis prior to1972*	Chronic hepatitis B infection	• Residence in hyper-endemic area • High risk health behavior(s): IV drug use; unprotected sex; multiple partners; high-risk sexual behavior; sexually transmitted disease; tattoos; body piercing	• Hepatitis B surface antigen (HBsAg)§ • Hepatitis B core antibody (anti HBc or HBcAb)	1
Diagnosis prior to 1993*	Chronic hepatitis C infection		• Hepatitis C antibody • Hepatitis C PCR (once in patients with positive hepatitis C antibody)	1

*Dates may differ in non U.S. treatment locations;

§Screen once following end of all cancer treatment or upon entry in long-term followup unless ongoing risk factors;

#Guideline recommendations scored “Category 1” reflecting uniform consensus of high level evidence among panel of late effects experts (see Table I);

**COG Health Link: http://www.survivorshipguidelines.org/pdf/Hepatitis.pdf