Conclusions of evidence from the systematic literature search for hepatic toxicity to inform surveillance for childhood, adolescent and young adult cancer survivors

Who needs surveillance for hepatic toxicity?	
Risk of clinical liver disease in CAYA cancer survivors	**Quality of evidence**
Unknown risk of clinical liver disease (fibrosis, cirrhosis, liver failure, biliary tract injury) confirmed by liver histology and/or imaging	No studies
Risk of cellular liver injury (elevated ALT) in CAYA cancer survivors	**Quality of evidence**
Unknown risk in survivors vs. general population	No studies
Increased risk after *radiotherapy to fields exposing the liver* vs. no radiotherapy	⊕⊕⊕⊕ HIGH [29, 30]
Unknown risk after *higher doses of radiotherapy to fields exposing the liver* vs. lower doses	No studies
Increased risk after *larger irradiated liver volumes* vs. smaller volumes	⊕⊕⊖⊖ LOW [29]
Increased risk after *busulfan* vs. no busulfan	⊕⊕⊖⊖ LOW [29, 30]
Increased risk after *thioguanine* vs. no thioguanine	⊕⊕⊖⊖ LOW [29, 30]
No significant effect of *mercaptopurine* vs. no mercaptopurine	⊕⊕⊕⊖ MODERATE [29, 30]
No significant effect of *methotrexate* vs. no methotrexate	⊕⊕⊕⊖ MODERATE [29, 30]
No significant effect of *dactinomycin* vs. no dactinomycin	⊕⊕⊕⊖ MODERATE [29, 30]
Unknown risk after *novel agents* (tyrosine kinase inhibitors, demethylating agents, monoclonal antibodies) vs. no novel agents	No studies
Unknown risk in cancer survivors after *HSCT* vs. no HSCT	No studies
Increased risk after *hepatic surgery* vs. no hepatic surgery	⊕⊕⊖⊖ LOW [29, 30]
Increased risk after *chronic viral hepatitis C* vs. no chronic viral hepatitis C	⊕⊕⊖⊖ LOW [29]
Unknown risk in cancer survivors with *iron overload* vs. without iron overload	No studies
Risk of biliary tract injury (elevated gGT) in CAYA cancer survivors	**Quality of evidence**
Unknown risk in survivors vs. general population	No studies
Increased risk after *radiotherapy with fields exposing the liver* vs. no radiotherapy	⊕⊕⊕⊖ MODERATE [30]
Unknown risk after *higher doses radiotherapy with fields exposing the liver* vs. lower doses	No studies
Unknown risk after *larger irradiated liver volumes* vs. smaller volumes	No studies
No significant effect of *busulfan* vs. no busulfan	⊕⊕⊖⊖ LOW [30]
No significant effect of *thioguanine* vs. no thioguanine	⊕⊕⊕⊖ MODERATE [30]
No significant effect of *mercaptopurine* vs. no mercaptopurine	⊕⊕⊕⊖ MODERATE [30]
No significant effect of *methotrexate* vs. no methotrexate	⊕⊕⊕⊖ MODERATE [30]
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Unknown risk after *novel agents* (tyrosine kinase inhibitors, demethylating agents, monoclonal antibodies) vs. no novel agents	No studies
Unknown risk after *HSCT* vs. no HSCT	No studies
No significant effect of *hepatic surgery* vs. no hepatic surgery	⊕⊕⊖⊖ LOW [30]
Unknown risk after *chronic viral hepatitis* vs. no chronic viral hepatitis	No studies
Unknown risk in cancer survivors with *iron overload* vs. without iron overload	No studies
Risk of iron overload in CAYA cancer survivors	**Quality of evidence**

Increased risk with increasing *packed red blood cell volume* (liver iron concentration by T2* MRI)	⊕⊖⊖⊖ VERY LOW [52]
Unknown *packed red blood cell volume* threshold for increased risk	No studies
Unknown risk after *HSCT* vs. no HSCT	No studies
No significant effect of *TBI* vs. no TBI in HSCT survivors (serum ferritin)	⊕⊖⊖⊖ VERY LOW [57]
When should surveillance for hepatic toxicity be initiated?	
Latency time in CAYA cancer survivors	**Quality of evidence**
Unknown latency time of developing clinical liver disease	No studies
At what frequency should surveillance for hepatic toxicity be performed?	
Risk over time in CAYA cancer survivors	**Quality of evidence**
Unknown course of abnormal liver enzymes and liver disease (fibrosis, cirrhosis, liver failure, biliary tract injury) over time after cancer treatment	No studies
Transfusion-related increased serum ferritin levels decline over time in HSCT survivors*	⊕⊕⊕⊖ MODERATE [56, 57]
What surveillance modality should be used for the detection of hepatic toxicity?	
Diagnostic value of liver function tests to detect clinical liver disease in CAYA cancer survivors	**Quality of evidence**
Unknown diagnostic value of liver enzymes (ALT, AST, gGT, ALP) and bilirubin compared to liver biopsy	No studies
Unknown diagnostic value of liver ultrasound or elastography compared to liver biopsy	No studies
Unknown diagnostic value of ferritin compared to liver biopsy or T2* MRI	No studies
What should be done when abnormalities are identified?	
Effectiveness of interventions in CAYA cancer survivors with abnormal liver function tests	**Quality of evidence**
Unknown effect of interventions to improve health	No studies

Abbreviations: CAYA: childhood, adolescent and young adult; ALT: alanine aminotransferase; HSCT: hematopoietic stem cell transplantation; gGT: gamma-glutamyltransferase; TBI: total body irradiation; MRI: magnetic resonance imaging; AST: aspartate aminotransferase; ALP: alkaline phosphatase

***** Without any intervention to improve iron status.