Summary of findings tables, grading of the evidence and detailed conclusions of evidence hepatic toxicity surveillance

Who needs surveillance?

No studies identified investigating the risk of fibrosis or cirrhosis confirmed by liver histology and/or imaging.

Cellular liver injury and biliary tract injury

PICO 1: No studies identified investigating the risk of cellular liver injury and biliary tract injury in CAYA cancer survivors vs. non-cancer survivors.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy RT exposing liver HSCT	Events	Effect size	Risk of bias
2a. Risk cellular liver injury after dactinomycin (n=2 studies)	Mulder 2013	1,362 CCS	12.4 (5.0-36.1)	Dactinomycin 29.1%; RT: 9.0%; HSCT: 4.5%	79 (5.8%) ALT > upper limit of normal (≥ 34 U/L for females, ≥ 45 U/L for males and children < 15 years)	Odds ratio (95% CI) Dactinomycin yes vs. no: 0.71 (0.29-1.76)	SB: low risk AB: low risk DB: unclear CF: low risk
	Green 2019	2,751 CCS	23.2 (interquartile range 17.6-29.7)	Dactinomycin: 14.5%; RT: 15.9%; HSCT: 2.8%	1,137 (41.3%) ALT > upper limit of normal (≥ 19 U/L for females, ≥ 30 U/L for males)	No significant effect of dactinomycin in univariable analysis and therefore not included in the multivariable model	SB: high risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 2/2; Detection bias unclear in 2/2 but the outcome measurement was not likely to be influenced by lack of blinding; Confounding low in 2/2
Consistency:	0	No important inconsistency: both studies showed a non-significant effect
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision: narrow confidence interval in 1 study, although in 1 study unclear
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		No significant effect of dactinomycin on the risk of cellular liver injury (elevated ALT) in CAYA cancer survivors. (2 studies no significant effect; 4,113 participants; 1,216 events)

Abbreviations: AB, attrition bias; ALT, alanine aminotransferase; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; HSCT, hematopoietic stem cell transplantation; RT, radiotherapy; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy RT exposing liver HSCT	Events	Effect size	Risk of bias
2b. Risk biliary tract injury after dactinomycin (n=1 study)	Mulder 2013	1,295 CCS	12.4 (5.0-36.1)	Dactinomycin 29.1%; RT: 9.0%; HSCT: 4.5%	68 (5.3%) gGT > upper limit of normal (≥ 40 U/L for females, ≥ 60 U/L for males, ≥ 56 U/L for children < 15 years)	Odds ratio (95% CI) Dactinomycin yes vs. no: 0.46 (0.17-1.21)	SB: low risk AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Retrospective cohort study					
Study limitations:	0	No important limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1 but the outcome measurement was not likely to be influenced by lack of blinding; Confounding low in 1/1					
Consistency:	0	Not applicable (1 study)					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-1	Some imprecision: only 1 study performed but narrow confidence interval					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	Unclear dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊕⊕⊖ MODERATE					
Conclusion:		No significant effect of dactinomycin on the risk of biliary tract injury (elevated gGT) in CAYA cancer survivors. (1 study no significant effect; 1,295 participants; 68 events)					

Abbreviations: AB, attrition bias; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; gGT, gamma-glutamyltransferase; HSCT, hematopoietic stem cell transplantation; RT, radiotherapy; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy RT exposing liver HSCT	Events	Effect size	Risk of bias
3a. Risk cellular liver injury after busulfan (n=2 studies)	Mulder 2013	1,362 CCS	12.4 (5.0-36.1)	Busulfan: 0.7%; RT: 9.0%; HSCT: 4.5%	79 (5.8%) ALT > upper limit of normal (≥ 34 U/L for females, ≥ 45 U/L for males and children < 15 years)	Odds ratio (95% CI) Busulfan yes vs. no: 3.9 (0.29-32.90)	SB: low risk AB: low risk DB: unclear CF: low risk
	Green 2019	2,751 CCS	23.2 (interquartile range 17.6-29.7)	Busulfan: 0.8%; RT: 15.9%; HSCT: 2.8%	1,137 (41.3%) ALT > upper limit of normal (≥ 19 U/L for females, ≥ 30 U/L for males)	Relative risk (95% CI) Busulfan yes vs. no: 1.54 (1.02-2.33)	SB: high risk AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Retrospective cohort studies					

Study limitations:	-1	Some limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 2/2; Detection bias unclear in 2/2 but the outcome measurement was not likely to be influenced by lack of blinding; Confounding low in 2/2
Consistency:	0	No important inconsistency: both studies showed an increased risk of busulfan (1 non-significant)
Directness:	0	Results are direct: population and outcomes broadly generalizable
Precision:	-1	Important imprecision: wide confidence interval in 1 study and the effect estimate did not reach the clinical decision threshold (RR=2) in 1 study
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Increased risk of cellular liver injury (elevated ALT) after busulfan in CAYA cancer survivors. (1 study significant effect, 1 study no significant effect; 4,113 participants; 1,216 events)

Abbreviations: AB, attrition bias; ALT, alanine aminotransferase; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; HSCT, hematopoietic stem cell transplantation; RT, radiotherapy; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy RT exposing liver HSCT	Events	Effect size	Risk of bias
3b. Risk biliary tract injury after busulfan (n=1 study)	Mulder 2013	1,295 CCS	12.4 (5.0-36.1)	Busulfan: 0.7%; RT: 9.0%; HSCT: 4.5%	68 (5.3%) gGT > upper limit of normal (≥ 40 U/L for females, ≥ 60 U/L for males, ≥ 56 U/L for children < 15 years)	Odds ratio (95% CI) Busulfan yes vs. no: 4.03 (0.33-48.94)	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Retrospective cohort study
Study limitations:	0	No important limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1 but the outcome measurement was not likely to be influenced by lack of blinding; Confounding low in 1/1
Consistency:	0	Not applicable (1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision: only 1 study performed and wide confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant effect of busulfan on the risk of biliary tract injury (elevated gGT) in CAYA cancer survivors. (1 study no significant effect; 1,295 participants; 68 events)

Abbreviations: AB, attrition bias; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; gGT, gamma-glutamyltransferase; HSCT, hematopoietic stem cell transplantation; RT, radiotherapy; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy RT exposing liver HSCT	Events	Effect size	Risk of bias
4a. Risk cellular liver injury after methotrexate (n=2 studies)	Mulder 2013	1,362 CCS	12.4 (5.0-36.1)	Methotrexate: 28.8%; RT: 9.0%; HSCT: 4.5%	79 (5.8%) ALT > upper limit of normal (≥ 34 U/L for females, ≥ 45 U/L for males and children < 15 years)	Odds ratio (95% CI) Methotrexate yes vs. no: 1.22 (0.53-2.84)	SB: low risk AB: low risk DB: unclear CF: low risk
	Green 2019	2,751 CCS	23.2 (interquartile range 17.6-29.7)	Methotrexate: 48.3%; RT: 15.9%; HSCT: 2.8%	1,137 (41.3%) ALT > upper limit of normal (≥ 19 U/L for females, ≥ 30 U/L for males)	No significant effect of methotrexate in univariable analysis and therefore not included in the multivariable model	SB: high risk AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Retrospective cohort studies					
Study limitations:	-1	Some limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 2/2; Detection bias unclear in 2/2 but the outcome measurement was not likely to be influenced by lack of blinding; Confounding low in 2/2					
Consistency:	0	No important inconsistency: both studies showed a non-significant effect					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	0	No important imprecision: narrow confidence interval in 1 study, although in 1 study unclear					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	Unclear dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊕⊕⊖ MODERATE					
Conclusion:		No significant effect of methotrexate on the risk of cellular liver injury (elevated ALT) in CAYA cancer survivors. (2 studies no significant effect; 4,113 participants; 1,216 events)					

Abbreviations: AB, attrition bias; ALT, alanine aminotransferase; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; HSCT, hematopoietic stem cell transplantation; RT, radiotherapy; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy RT exposing liver HSCT	Events	Effect size	Risk of bias
4b. Risk biliary tract injury after methotrexate (n=1 study)	Mulder 2013	1,295 CCS	12.4 (5.0-36.1)	Methotrexate: 28.8%; RT: 9.0%; HSCT: 4.5%	68 (5.3%) gGT > upper limit of normal (≥ 40 U/L for females, ≥ 60 U/L for males, ≥ 56 U/L for children < 15 years)	Odds ratio (95% CI) Methotrexate yes vs. no: 0.70 (0.27-1.81)	SB: low risk AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Retrospective cohort study					

Study limitations:	0	No important limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1 but the outcome measurement was not likely to be influenced by lack of blinding; Confounding low in 1/1
Consistency:	0	Not applicable (1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision: only 1 study performed but narrow confidence interval
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		No significant effect of methotrexate on the risk of biliary tract injury (elevated gGT) in CAYA cancer survivors. (1 study no significant effect; 1,295 participants; 68 events)

Abbreviations: AB, attrition bias; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; gGT, gamma-glutamyltransferase; HSCT, hematopoietic stem cell transplantation; RT, radiotherapy; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy RT exposing liver HSCT	Events	Effect size	Risk of bias
5a. Risk cellular liver injury after mercaptopurine (n=2 studies)	Mulder 2013	1,362 CCS	12.4 (5.0-36.1)	Mercaptopurine: 25.8%; RT: 9.0%; HSCT: 4.5%	79 (5.8%) ALT > upper limit of normal (≥ 34 U/L for females, ≥ 45 U/L for males and children < 15 years)	Odds ratio (95% CI) Mercaptopurine yes vs. no: 0.84 (0.36-1.99)	SB: low risk AB: low risk DB: unclear CF: low risk
	Green 2019	2,751 CCS	23.2 (interquartile range 17.6-29.7)	Mercaptopurine: 39.0%; RT: 15.9%; HSCT: 2.8%	1,137 (41.3%) ALT > upper limit of normal (≥ 19 U/L for females, ≥ 30 U/L for males)	No significant effect of mercaptopurine in univariable analysis and therefore not included in the multivariable model	SB: high risk AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Retrospective cohort studies					
Study limitations:	-1	Some limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 2/2; Detection bias unclear in 2/2 but the outcome measurement was not likely to be influenced by lack of blinding; Confounding low in 2/2					
Consistency:	0	No important inconsistency: both studies showed a non-significant effect					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	0	No important imprecision: narrow confidence interval in 1 study, although in 1 study unclear					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	Unclear dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊕⊕⊖ MODERATE					
Conclusion:		No significant effect of mercaptopurine on the risk of cellular liver injury (elevated ALT) in CAYA cancer survivors. (2 studies no significant effect; 4,113 participants; 1,216 events)					

Abbreviations: AB, attrition bias; ALT, alanine aminotransferase; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; HSCT, hematopoietic stem cell transplantation; RT, radiotherapy; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy RT exposing liver HSCT	Events	Effect size	Risk of bias
5b. Risk biliary tract injury after mercaptopurine (n=1 study)	Mulder 2013	1,295 CCS	12.4 (5.0-36.1)	Mercaptopurine: 25.8%; RT: 9.0%; HSCT: 4.5%	68 (5.3%) gGT > upper limit of normal (≥ 40 U/L for females, ≥ 60 U/L for males, ≥ 56 U/L for children < 15 years)	Odds ratio (95% CI) Mercaptopurine yes vs. no: 0.64 (0.25-1.64)	SB: low risk AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Retrospective cohort study					
Study limitations:	0	No important limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1 but the outcome measurement was not likely to be influenced by lack of blinding; Confounding low in 1/1					
Consistency:	0	Not applicable (1 study)					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-1	Some imprecision: only 1 study performed but narrow confidence interval					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	Unclear dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊕⊕⊖ MODERATE					
Conclusion:		No significant effect of mercaptopurine on the risk of biliary tract injury (elevated gGT) in CAYA cancer survivors. (1 study no significant effect; 1,295 participants; 68 events)					

Abbreviations: AB, attrition bias; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; gGT, gamma-glutamyltransferase; HSCT, hematopoietic stem cell transplantation; RT, radiotherapy; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy RT exposing liver HSCT	Events	Effect size	Risk of bias
6a. Risk cellular liver injury after thioguanine (n=2 studies)	Mulder 2013	1,362 CCS	12.4 (5.0-36.1)	Thioguanine: 7.2%; RT: 9.0%; HSCT: 4.5%	79 (5.8%) ALT > upper limit of normal (≥ 34 U/L for females, ≥ 45 U/L for males and children < 15 years)	Odds ratio (95% CI) Thioguanine yes vs. no: 1.40 (0.38-5.18)	SB: low risk AB: low risk DB: unclear CF: low risk
	Green 2019	2,751 CCS	23.2 (interquartile range 17.6-29.7)	Thioguanine: 0.9%; RT: 15.9%; HSCT: 2.8%	1,137 (41.3%) ALT > upper limit of normal (≥ 19 U/L for females, ≥ 30 U/L for males)	Relative risk (95% CI) Thioguanine yes vs. no: 1.38 (1.02-1.85)	SB: high risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 2/2; Detection bias unclear in 2/2 but the outcome measurement was not likely to be influenced by lack of blinding; Confounding low in 2/2
Consistency:	0	No important inconsistency: both studies showed an increased risk of thioguanine (1 non-significant)
Directness:	0	Results are direct: population and outcomes broadly generalizable
Precision:	-1	Some imprecision: wide confidence intervals in 1 study and the effect estimate did not reach the clinical decision threshold (RR=2) in 1 study
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Increased risk of cellular liver injury (elevated ALT) after thioguanine in CAYA cancer survivors. (1 study significant effect, 1 study no significant effect; 4,113 participants; 1,216 events)

Abbreviations: AB, attrition bias; ALT, alanine aminotransferase; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; HSCT, hematopoietic stem cell transplantation; RT, radiotherapy; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy RT exposing liver HSCT	Events	Effect size	Risk of bias
6b. Risk biliary tract injury after thioguanine (n=1 study)	Mulder 2013	1,295 CCS	12.4 (5.0-36.1)	Thioguanine: 7.2%; RT: 9.0%; HSCT: 4.5%	68 (5.3%) gGT > upper limit of normal (≥ 40 U/L for females, ≥ 60 U/L for males, ≥ 56 U/L for children < 15 years)	Odds ratio (95% CI) Thioguanine yes vs. no: 0.51 (0.09-2.80)	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Retrospective cohort study
Study limitations:	0	No important limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1 but the outcome measurement was not likely to be influenced by lack of blinding; Confounding low in 1/1
Consistency:	0	Not applicable (1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some imprecision: only 1 study performed but narrow confidence interval
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		No significant effect of thioguanine on the risk of biliary tract injury (elevated gGT) in CAYA cancer survivors. (1 study no significant effect; 1,295 participants; 68 events)

Abbreviations: AB, attrition bias; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; gGT, gamma-glutamyltransferase; HSCT, hematopoietic stem cell transplantation; RT, radiotherapy; SB, selection bias; yr, year.

PICO 7: No studies identified investigating the risk of cellular liver injury and biliary tract injury in CAYA cancer survivors treated with novel agents (e.g. tyrosine kinase inhibitors, demethylating agents, monoclonal antibodies).

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy RT exposing liver HSCT	Events	Effect size	Risk of bias
8.1a. Risk cellular liver injury after radiotherapy to liver (n=2 studies)	Mulder 2013	1,362 CCS	12.4 (5.0-36.1)	Chemotherapy: 88.4%; RT: 9.0%; HSCT: 4.5%	79 (5.8%) ALT > upper limit of normal (≥ 34 U/L for females, ≥ 45 U/L for males and children < 15 years)	Odds ratio (95% CI) Radiotherapy to liver yes vs. no: 2.34 (1.07-5.13)	SB: low risk AB: low risk DB: unclear CF: low risk
	Green 2019	2,751 CCS	23.2 (interquartile range 17.6-29.7)	Chemotherapy: at least 48.3%; RT: 15.9%; HSCT: 2.8%	1,137 (41.3%) ALT > upper limit of normal (≥ 19 U/L for females, ≥ 30 U/L for males)	Relative risk (95% CI) Radiotherapy to liver treated to ≥ 15 Gy per 10% volume increase: 1.06 (1.03-1.08)	SB: high risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 2/2; Detection bias unclear in 2/2 but the outcome measurement was not likely to be influenced by lack of blinding; Confounding low in 2/2
Consistency:	0	No important inconsistency: both studies showed a significantly increased risk of radiotherapy
Directness:	0	Results are direct: population and outcomes broadly generalizable
Precision:	0	No important imprecision: narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect (RR >2)
Dose-response:	0	Unclear dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⨁ HIGH
Conclusion:		Increased risk of cellular liver injury (elevated ALT) after radiotherapy involving fields exposing the liver in CAYA cancer survivors. (2 studies significant effect; 4,113 participants; 1,216 events)

Abbreviations: AB, attrition bias; ALT, alanine aminotransferase; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; HSCT, hematopoietic stem cell transplantation; RT, radiotherapy; SB, selection bias; yr, year.

PICO 8.2a: No studies identified investigating the risk of cellular liver injury in CAYA cancer survivors treated with higher vs. lower doses of radiotherapy to fields exposing the liver.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy RT exposing liver HSCT	Events	Effect size	Risk of bias
8.3a. Risk cellular liver injury after larger vs. smaller	Green 2019	2,751 CCS	23.2 (interquartile range 17.6-29.7)	Chemotherapy: at least 48.3%; RT: 15.9%;	1,137 (41.3%) ALT > upper limit of normal (≥ 19 U/L for	Relative risk (95% CI) Radiotherapy to liver treated to ≥ 15 Gy per 10% volume increase:	SB: high risk AB: low risk DB: unclear

radiotherapy volumes to liver (n=1 study)			HSCT: 2.8%	females, ≥ 30 U/L for males)	1.06 (1.03-1.08)	CF: low risk
GRADE assessment:						
Study design:	+4	Retrospective cohort study				
Study limitations:	-1	Some limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1 but the outcome measurement was not likely to be influenced by lack of blinding; Confounding low in 1/1				
Consistency:	0	Not applicable (1 study)				
Directness:	0	Results are direct: population and outcomes broadly generalizable				
Precision:	-1	Some imprecision: only 1 study performed but narrow confidence interval				
Publication bias:	0	Unlikely				
Effect size:	0	No large magnitude of effect				
Dose-response:	0	Unclear dose response relationship				
Plausible confounding:	0	No plausible confounding				
Quality of evidence:		⊕⊕⊖⊖ LOW				
Conclusion:		Increased risk of cellular liver injury (elevated ALT) after larger irradiated liver volumes in CAYA cancer survivors. (1 study significant effect; 2,751 participants; 1,137 events)				

Abbreviations: AB, attrition bias; ALT, alanine aminotransferase; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; HSCT, hematopoietic stem cell transplantation; RT, radiotherapy; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy RT exposing liver HSCT	Events	Effect size	Risk of bias
8.1b. Risk biliary tract injury after radiotherapy to liver (n=1 study)	Mulder 2013	1,295 CCS	12.4 (5.0-36.1)	Chemotherapy: 88.4%; RT: 9.0%; HSCT: 4.5%	68 (5.3%) gGT > upper limit of normal (≥ 40 U/L for females, ≥ 60 U/L for males, ≥ 56 U/L for children < 15 years)	Odds ratio (95% CI) Radiotherapy to fields involving the liver yes vs. no: 5.45 (2.51-11.82)	SB: low risk AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Retrospective cohort study					
Study limitations:	0	No important limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1 but the outcome measurement was not likely to be influenced by lack of blinding; Confounding low in 1/1					
Consistency:	0	Not applicable (1 study)					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-2	Important imprecision: only 1 study performed and wide confidence interval					
Publication bias:	0	Unlikely					
Effect size:	+1	Large magnitude of effect					
Dose-response:	0	Unclear dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊕⊕⊖ MODERATE					
Conclusion:		Increased risk of biliary tract injury (elevated gGT) after radiotherapy involving fields exposing the liver in CAYA cancer survivors.					

	(1 study significant effect; 1,295 participants; 68 events)

Abbreviations: AB, attrition bias; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; HSCT, hematopoietic stem cell transplantation; RT, radiotherapy; SB, selection bias; yr, year.

PICO 8.2b: No studies identified investigating the risk of biliary tract injury in CAYA cancer survivors treated with higher vs. lower doses of radiotherapy to fields exposing the liver.

PICO 8.3b: No studies identified investigating the risk of biliary tract injury in CAYA cancer survivors treated with larger vs. smaller radiotherapy volumes to the liver.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy RT exposing liver HSCT	Events	Effect size	Risk of bias
9a. Risk cellular liver injury after hepatic surgery (n=2 studies)	Mulder 2013	1,362 CCS	12.4 (5.0-36.1)	Chemotherapy: 88.4%; RT: 9.0%; HSCT: 4.5%	79 (5.8%) ALT > upper limit of normal (≥ 34 U/L for females, ≥ 45 U/L for males and children < 15 years)	Odds ratio (95% CI) Liver resection yes vs. no: 1.87 (0.38-9.07)	SB: low risk AB: low risk DB: unclear CF: low risk
	Green 2019	2,751 CCS	23.2 (interquartile range 17.6-29.7)	Chemotherapy: at least 48.3%; RT: 15.9%; HSCT: 2.8%	1,137 (41.3%) ALT > upper limit of normal (≥ 19 U/L for females, ≥ 30 U/L for males)	Relative risk (95% CI) Hepatic surgery yes vs. no: 1.90 (1.45-2.49)	SB: high risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 2/2; Detection bias unclear in 2/2 but the outcome measurement was not likely to be influenced by lack of blinding; Confounding low in 2/2
Consistency:	0	No important inconsistency: both studies showed an increased risk of hepatic surgery (1 non-significant)
Directness:	0	Results are direct: population and outcomes broadly generalizable
Precision:	-1	Some imprecision: wide confidence interval in 1 study and the effect estimate did not reach the clinical decision threshold (RR=2) in 1 study
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Increased risk of cellular liver injury (elevated ALT) after hepatic surgery in CAYA cancer survivors. (1 study significant effect, 1 study no significant effect; 4,113 participants; 1,216 events)

Abbreviations: AB, attrition bias; ALT, alanine aminotransferase; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; HSCT, hematopoietic stem cell transplantation; RT, radiotherapy; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy RT exposing liver HSCT	Events	Effect size	Risk of bias
9b. Risk biliary tract injury after hepatic surgery (n=1 study)	Mulder 2013	1,295 CCS	12.4 (5.0-36.1)	Chemotherapy: 88.4%; RT: 9.0%; HSCT: 4.5%	68 (5.3%) gGT > upper limit of normal (≥ 40 U/L for females, ≥ 60 U/L for males, ≥ 56 U/L for children < 15 years)	Odds ratio (95% CI) Liver resection yes vs. no: 1.09 (0.12-9.69)	SB: low risk AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Retrospective cohort study					
Study limitations:	0	No important limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1 but the outcome measurement was not likely to be influenced by lack of blinding; Confounding low in 1/1					
Consistency:	0	Not applicable (1 study)					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-2	Important imprecision: only 1 study performed and wide confidence interval					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	Unclear dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊕⊖⊖ LOW					
Conclusion:		No significant effect of hepatic surgery on the risk of biliary tract injury (elevated gGT) in CAYA cancer survivors. (1 study no significant effect; 1,295 participants; 68 events)					

Abbreviations: AB, attrition bias; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; gGT, gamma-glutamyltransferase; HSCT, hematopoietic stem cell transplantation; RT, radiotherapy; SB, selection bias; yr, year

PICO 10: No studies identified investigating the risk of cellular liver injury and biliary tract injury in CAYA cancer survivors treated with HSCT vs. no HSCT.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy RT exposing liver HSCT	Events	Effect size	Risk of bias
10. Risk cellular liver injury after HSCT (n=1 study)	Green 2019	2,751 CCS	23.2 (interquartile range 17.6-29.7)	Chemotherapy: at least 48.3%; RT: 15.9%; HSCT: 2.8%	1,137 (41.3%) ALT > upper limit of normal (≥ 19 U/L for females, ≥ 30 U/L for males)	No significant effect of HSCT in univariable analysis and therefore not included in the multivariable model	SB: high risk AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Retrospective cohort study					
Study limitations:	-1	Some limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1 but the outcome measurement was not likely to be influenced by lack of blinding; Confounding low in 1/1					
Consistency:	0	Not applicable (1 study)					
Directness:	0	Results are direct: population and outcomes broadly generalizable					
Precision:	-1	Some imprecision: only 1 study performed					

Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant effect of HSCT on the risk of cellular liver injury (elevated ALT) in CAYA cancer survivors. (1 study no significant effect; 2,751 participants; 1,137 events)

Abbreviations: AB, attrition bias; ALT, alanine aminotransferase; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; HSCT, hematopoietic stem cell transplantation; RT, radiotherapy; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy RT exposing liver HSCT	Events	Effect size	Risk of bias
11a. Risk cellular liver injury by chronic viral hepatitis (n=1 study)	Green 2019	2,751 CCS	23.2 (interquartile range 17.6-29.7)	Chemotherapy: at least 48.3%; RT: 15.9%; HSCT: 2.8%	1,137 (41.3%) ALT > upper limit of normal (≥ 19 U/L for females, ≥ 30 U/L for males)	Relative risk (95% CI) Hepatitis C grade ≥1 vs. <1: 1.76 (1.52-2.02)	SB: high risk AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Retrospective cohort study					
Study limitations:	-1	Some limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1 but the outcome measurement was not likely to be influenced by lack of blinding; Confounding low in 1/1					
Consistency:	0	Not applicable (1 study)					
Directness:	0	Results are direct: population and outcomes broadly generalizable					
Precision:	-1	Some imprecision: only 1 study performed and the effect estimate did not reach the clinical decision threshold (RR=2); but narrow confidence interval					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	Unclear dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊕⊖⊖ LOW					
Conclusion:		Increased risk of cellular liver injury (elevated ALT) after chronic viral hepatitis C (grade ≥1) in CAYA cancer survivors. (1 study significant effect; 2,751 participants; 1,137 events)					
Note:		In the Cochrane systematic review of Mulder et al. chronic viral hepatitis was shown to increase the risk of cellular liver injury in 6 univariable studies.					

Abbreviations: AB, attrition bias; ALT, alanine aminotransferase; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; HSCT, hematopoietic stem cell transplantation; RT, radiotherapy; SB, selection bias; yr, year.

PICO 11b: No studies identified investigating the risk of biliary tract injury in CAYA cancer survivors with chronic viral hepatitis or multiple blood product transfusions prior to blood product screening.

PICO 12: No studies identified investigating the risk of cellular liver injury in CAYA cancer survivors with iron overload.

Iron overload

PICO 13: No studies identified investigating the risk of iron overload in CAYA cancer survivors vs. non-cancer survivors.

PICO 14: No studies identified investigating the risk of iron overload in CAYA cancer survivors treated with HSCT vs. no HSCT.
Note: Two studies (Chotsampancharoen 2009 and Sirvent 2017) included only CAYA cancer survivors treated with HSCT. These studies showed that HSCT survivors are at risk for iron overload.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy RT exposing liver HSCT	Events	Effect size	Risk of bias
15. Risk iron overload after red blood cell transfusions (n=1 study)	Ruccione 2014	73 CCS	4.4 (0.2-7.6)	HSCT: 5.3%; Other not reported	36 (49.3%) liver iron concentration by MRI >1.2mg/g	Risk factors for increased liver iron concentration: Weight-adjusted cumulative packed red blood cell volume associated with a 0.03 mg/g increase in LIC for each mL/kg transfused (p<0.0001)	SB: high risk AB: low risk DB: low risk CF: low risk
GRADE assessment:							
Study design:	+4	Retrospective cohort study					
Study limitations:	-1	Some limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding low in 1/1					
Consistency:	0	Not applicable (1 study)					
Directness:	0	Results are direct, population and outcomes broadly generalizable					
Precision:	-2	Important imprecision: only 1 study performed and small study population					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	Unclear dose response relationship					
Plausible confounding:	0	No plausible confounding					
Quality of evidence:		⊕⊖⊖⊖ VERY LOW					
Conclusion:		Increased risk of iron overload (liver iron concentration by MRI >1.2mg/g) after higher packed red blood cell volume. (1 study significant effect; 73 participants; 36 events)					

Abbreviations: AB, attrition bias; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; HSCT, hematopoietic stem cell transplantation; SB, selection bias; yr, year.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy RT exposing liver HSCT	Events	Effect size	Risk of bias
16. Risk iron overload after radiotherapy to liver (n=1 study)	Sirvent 2017	322 allogeneic HSCT childhood leukemia survivors	9.98 ± 0.35 (data of total group of HSCT survivors)	Busulfan: 33.1%; TBI: 66.9%; HSCT: 100% (data of total group of HSCT survivors)	Not reported for 322 with allogeneic HSCT; For total group including autologous HSCT: 162/384 (42.2%) serum ferritin level ≥350 ng/ml with an	*Serum ferritin level ≥350 ng/ml* Odds ratio (95% CI) TBI-based vs. busulfan-based regimen: 2.16 (0.93-5.01) *Serum ferritin level ≥1000 ng/ml* Odds ratio (95% CI)	SB: unclear AB: low risk DB: unclear CF: high risk

			erythrocyte sedimentation rate at an hour <50 mm; 51 (13.3%) Serum ferritin level ≥1000 ng/ml	TBI-based vs. busulfan-based regimen: 1.18 (0.40-3.48)	
GRADE assessment:					
Study design:	+4	Retrospective cohort study			
Study limitations:	-2	Important limitations: Selection bias unclear in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1 but the outcome measurement was not likely to be influenced by lack of blinding; Confounding high in 1/1			
Consistency:	0	Not applicable (1 study)			
Directness:	0	Results are direct, population and outcomes broadly generalizable			
Precision:	-1	Some imprecision: only 1 study performed			
Publication bias:	0	Unlikely			
Effect size:	0	No large magnitude of effect			
Dose-response:	0	Unclear dose response relationship			
Plausible confounding:	0	No plausible confounding			
Quality of evidence:		⊕⊖⊖⊖ VERY LOW			
Conclusion:		No significant effect of TBI on the risk of iron overload (serum ferritin ≥350 and ≥1000 ng/ml) in CAYA cancer survivors treated with allogeneic HSCT. (1 study no significant effect; 322 participants; events unknown)			

Abbreviations: AB, attrition bias; CF, confounding; DB, detection bias; HSCT, hematopoietic stem cell transplantation; TBI, total body irradiation; SB, selection bias; yr, year.

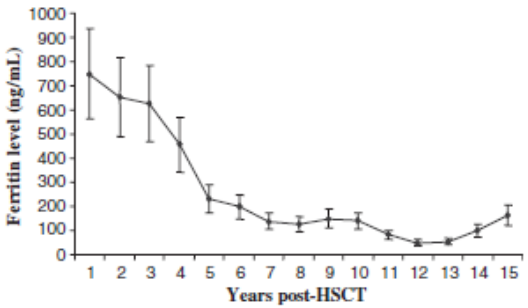
When should surveillance be initiated?

PICO 17: No studies identified investigating the latency time and its determinants of developing clinical liver disease in CAYA cancer survivors.

At what frequency should surveillance be performed?

PICO 18a and 18b: No studies identified investigating the risk of cellular liver injury and biliary tract injury over time and determinants of change in CAYA cancer survivors.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy RT exposing liver HSCT	Events	Effect size	Risk of bias
18c. Risk iron overload over time	Sirvent 2017	384 childhood leukemia survivors	9.98 ± 0.35	Busulfan: 33.1%; TBI: 66.9%; HSCT: 100%	68 survivors with untreated iron overload with at least 2 measurements	Mean serum ferritin levels decreased over time: 1st evaluation: 883 ng/ml 2nd evaluation: 581 ng/ml Mean 3.68 yr between evaluations	SB: unclear AB: low risk DB: unclear

(n=2 studies)	Chotsampancharoen 2009	133 CCS	5.6 (1-15)	Chemotherapy: NM TBI: 95.5% HSCT: 100%	124 (93.2%) Serum ferritin >110 ng/ml	Mean serum ferritin level declined over time 	SB: unclear AB: unclear DB: unclear

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias unclear in 2/2; Attrition bias low in 1/2, unclear in 1/2; Detection bias unclear in 2/2 but the outcome measurement was not likely to be influenced by lack of blinding
Consistency:	0	No important inconsistency: both studies showed a decrease in serum ferritin levels over time
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	Imprecision unclear
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		Serum ferritin levels decreased over time in CAYA cancer survivors treated with HSCT. (2 studies; 517 participants; 192 events)

Abbreviations: AB, attrition bias; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; HSCT, hematopoietic stem cell transplantation; NM, not mentioned; TBI, total body irradiation; SB, selection bias; yr, year.

What surveillance modality should be used?

PICOs 19-22: No studies identified investigating diagnostic values of liver function tests in CAYA cancer survivors.

What should be done when abnormalities are identified?

PICOs 23-24: No studies identified investigating effectiveness of interventions in CAYA cancer survivors with abnormal liver enzymes or iron overload.

Focal nodular hyperplasia and nodular regenerative hyperplasia in CAYA cancer survivors

Outcome	Study	No. and type of participants	Follow-up and age (median/mean, range) yr	Outcomes
25a. Incidence and natural course focal nodular hyperplasia n=7 studies	Cattoni 2020	105 childhood HSCT survivors that underwent T2*MRI (group A) and that underwent imaging performed for different clinical indications (group B)	Interval between primary cancer treatment and FNH diagnosis: - Mean 4.4 ± 3.1 yr (range 3.5-24.0 yr) after HSCT in total group - 3.5 ± 1.7 yr (range 13.6-24.0 yr) after HSCT in group A - 7.0 ± 1.7 yr (range 3.5-10.3 yr) after HSCT in group B Age at FNH diagnosis: - Range 16.3-35.5 yr - Range 16.3-26.0 yr in group A - Range 24.6-35.5 yr in group B	FNH - 12 in total - 9/105 (8.6%) in group A - 3 in group B Detection of FNH - 9/12 (75.0%) in group A by MRI for iron overload screening - 2/12 (16.7%) in group B by ultrasound for abdominal pain - 1/12 (8.3%) in group B by MRI for clinical follow-up - 9/12 (75.0%) multiple lesions - 12/12 (100%) normal liver function tests Etiologic factors - 10/12 (83.3%) HSCT for malignant disease - 10/12 (83.3%) allogeneic HSCT; 2/12 (16.7%) autologous HSCT - 5/12 (41.7%) TBI - 10/12 (83.3%) cyclophosphamide - 6/12 (50.0%) busulfan - 6/12 (50.0%) melphalan - 4/12 (33.3%) etoposide - 2/12 (16.7%) fludarabine - 6/7 (85.7%) of girls HRT - 2/12 (16.7%) severe chronic GVHD; 4/12 (33.3%) limited chronic GVHD - 2/12 (16.7%) liver GVHD - 1/12 (8.3%) VOD Risk factors for FNH in multivariable logistic regression analysis - Female vs. male: OR 2.58 (95% CI 0.50-13.10) - HRT yes vs. no: OR 7.93 (95% CI 1.32-47.68) - Chronic GVHD yes vs. no: OR 1.88 (95% CI 0.39-9.21) - Iron overload moderate/severe vs. none/mild: OR 4.61 (95% CI 0.80-26.68)

				- Age at HSCT, malignant disease, abdominal RT, chemotherapy, liver GVHD and VOD not significantly associated in univariable analyses <u>Natural course</u> - 12/12 (100%) alive at latest follow-up - 12/12 (100%) normal liver function tests at subsequent biochemical follow-up *Group A:* - 1/9 (11.1%) complete regression - 3/9 (33.3%) reduction in size and/or number of lesions - 3/9 (33.3%) increase in size and/or number of lesions - 2/9 (22.2%) nodules remained substantially unchanged after a mean radiological follow-up of 4.5 ± 3.3 yr (range 1.1-12.1 yr) - None of 39 nodules showed malignant transformation after a mean radiological follow-up of 4.5 ± 3.3 yr (range 1.1-12.1 yr)
	Pillon 2015	324 childhood HSCT survivors that underwent abdominal imaging before and after HSCT	<u>Interval between HSCT and FNH diagnosis:</u> Median 5.7 (range 3.1-11.4) yr <u>Age at FNH diagnosis:</u> Range 8.9-21.7 yr	<u>Prevalence of FNH</u> 17/324 (5.2%), of whom 1 with a non-cancer diagnosis <u>Detection of FNH</u> - 12/17 (70.6%) incidental finding during follow-up - 3/17 (17.6%) symptoms (right hypochondrium pain (n=1), asthenia and abdominal pain (n=2)) - 3/17 (17.6%) other reasons for imaging (not specified, but all altered liver function tests) - 0/17 (0%) palpable abdominal masses - 8/17 (47.1%) altered liver function tests (ALT, AST, gGT, ALP) - 11/17 (64.7%) multiple nodules <u>Etiologic factors</u> - 6/17 (35.3%) autologous HSCT, 11/17 (64.7%) allogeneic HSCT - 14/17 (82.4%) radiation involving the abdomen (abdominal RT (n=4), TBI (n=10) - 9/17 (52.9%) acute GVHD - 7/17 (41.2%) chronic GVHD (not involving liver) - 0/17 (0%) active chronic GVHD at time of FNH diagnosis - 0/0 (0%) SOS - 10/11 (90.9%) of girls HRT (2 started after development of FNH) <u>Risk factors for FNH in multivariable Cox regression analysis</u>

				- Age at HSCT ≤12 yr vs. >12 yr: HR 9.10 (95% CI 1.21-71.40) - HRT yes vs. no: HR 4.02 (95% CI 1.45-11.11) - Chronic GVHD yes vs. no: HR 2.99 (95% CI 1.04-8.57) - Abdominal RT yes vs. no: HR 4.37 (95% CI 1.28-14.94) <u>Natural course</u> - 6/17 (35.2%) biopsy - 1/17 (5.9%) underwent surgery - 9/17 (52.9%) fibrosis at FibroScan (1 with cirrhosis) - 17/17 (100%) alive at last follow-up (follow-up duration not reported) - 3/17 (17.6%) stable in time - 9/17 (52.9%) developed ≥1 additional lesions - 5/17 (29.4%) unknown due to short follow-up
	Masetti 2013a*	236 childhood cancer survivors that underwent abdominal imaging before and after cancer treatment	<u>Interval between primary cancer treatment and FNH diagnosis:</u> Range 4.4-10.6 yr <u>Age at FNH diagnosis:</u> Range 8.5-23.3 yr	<u>Prevalence of FNH</u> 10/236 (4.2%) <u>Detection of FNH</u> - 10/10 (100%) incidental finding during follow-up - 0/10 (0%) clinical or laboratory signs of disease progression - 1/10 (10%) symptoms (recurrent abdominal pain) - 1/10 (10%) slightly altered liver function tests (transaminase increase) - 9/10 (90%) multiple nodules <u>Etiologic factors</u> - 5/10 (50%) abdominal radiation - 8/10 (80%) HSCT (autologous (n=6), allogeneic (n=2)) <u>Risk factors for FNH and hemangioma (n=4) in multivariable Cox regression analysis</u> - HSCT yes vs. no: OR 4.34 (95% CI 1.34-17.7) - Abdominal RT yes vs. no: OR 4.21 (95% CI 1.19-16.0) <u>Natural course</u> - Median follow-up after FNH 3.8 years (2.3-7.2 years) - 2/10 (20%) biopsy - 2/10 (20%) increasing number of nodules - 0/10 (0%) malignant transformation
	Masetti 2013b*	87 childhood HSCT survivors that	<u>Interval</u>	<u>Prevalence of FNH</u> 10/87 (11.5%)

		underwent abdominal imaging before and after HSCT	<u>between HSCT and FNH diagnosis:</u> Median 7.0 (range 4.4-14.8) yr <u>Age at FNH diagnosis:</u> Range 9.9-23.3 yr	<u>Detection of FNH</u> - 10/10 (100%) follow-up ultrasound post-HSCT - 0/10 (0%) clinical or laboratory signs of primary disease progression - 1/10 (10%) symptoms (abdominal pain) - 1/10 (10%) slightly altered liver function tests (transaminase increase) <u>Etiologic factors</u> - 8/10 (80%) autologous HSCT, 2/10 (20%) allogeneic HSCT - 6/10 (60%) abdominal radiation - 5/10 (50%) TBI - 4/10 (40%) busulfan-based conditioning - 2/10 (20%) acute GVHD - 1/10 (10) chronic GVHD involving liver - 0/10 (0%) SOS <u>Natural course</u> - Follow-up time after FNH diagnosis: Median 3.8 (range 2.3-7.2) yr - 1/10 (10%) had increase in number of nodules (from 4 to 6) over 2 yr (size and radiologic characteristics of nodules were unchanged) - 1/10 (10%) had increase in size of lesion (from 12 to 15 mm)
	Smith 2012	273 childhood solid tumor survivors that underwent abdominal imaging before and after cancer treatment	<u>Interval between primary cancer treatment and FNH diagnosis:</u> Median 7.7 (range 3.7-19.8) yr <u>Age at FNH diagnosis:</u> Not reported	<u>Prevalence of FNH</u> 14/273 (5.1%) <u>Detection of FNH</u> 12/14 (85.7%) multiple lesions <u>Natural course</u> Follow-up time after FNH diagnosis: Median 9.6 (range 4.8-28.1) yr
	Sudour 2009	138 HSCT survivors that underwent abdominal imaging after HSCT 97/138 (70%) were <18 yr at diagnosis	<u>Interval between HSCT and FNH diagnosis:</u> Median 6.4 (range 2.2-13.6) yr <u>Age at FNH diagnosis:</u> Median 13.7 (range 8.9-22.9) yr	<u>Prevalence of FNH</u> 17/138 (12.3%), of whom all pediatric patients, and 2 with a non-cancer diagnosis <u>Detection of FNH</u> - 17/17 (100%) follow-up imaging for evaluation of hemochromatosis (MRI to assess liver iron concentration) - 0/10 (0%) symptoms

				- 1/10 (10%) altered liver function tests in survivor with concomitant hepatic chronic GVHD - 13/17 (76.5%) multiple lesions <u>Etiologic factors</u> - 5/17 (29.4%) autologous HSCT, 12/17 (70.6%) allogeneic HSCT - 10/17 (58.8%) TBI - 6/17 (35.3%) busulfan-based regimen - 7/17 (41.2%) melphalan-based regimen - 8/17 (47.1%) cyclophosphamide-based regimen - 2/17 (11.8%) acute GVHD - 3/17 (17.6%) SOS - 16/17 (94.1%) hemochromatosis - 6/11 (54.5%) of females used oral contraception <u>Risk factors for FNH in multivariable Cox regression analysis</u> - Age <18 yr vs. >18 yr: HR 9.20 (95% CI 1.17-72.46) - Disease status high risk vs. low risk (definition not reported): HR 2.72 (95% CI 0.95-7.89) - Gender, type of conditioning regimen (myeloablative versus nonmyeloablative) type of transplant (autologous versus allogeneic), type of donor, source of graft, SOS, GVHD, hemochromatosis of the liver and type of GVHD prophylaxis were not significantly associated <u>Natural course</u> - 16/17 (94.1%) alive a median 3.9 (range 0.5-9.3) yr since FNH diagnosis - 1/17 (5.9%) died due to extensive chronic GVHD - 3/17 (17.6%) underwent biopsy and had regenerative nodules - 5/12 (41.7%) with radiological follow-up had increase in size of lesion - 1/12 (8.3%) with radiological follow-up had an additional lesion - 0/12 (0.0%) with radiological follow-up had malignant transformation
	De Bouyn 2003	3098 childhood cancer patients with a solid tumor that underwent abdominal ultrasound examinations; unclear how many survivors	<u>Interval between primary cancer treatment and FNH diagnosis:</u> Median 8.5 (range 4-21) yr <u>Age at FNH diagnosis:</u>	<u>Prevalence of FNH</u> 14/3098 (0.45%) <u>Detection of FNH</u> - 11/14 (78.6%) routine imaging examination - 3/14 (21.4%) abdominal pain - 0/14 (10%) abnormal liver function tests - 4/14 (28.6%) multiple lesions

	Range 7-23 yr	<u>Etiologic factors</u> - 3/14 (21.4%) radiotherapy to fields involving the liver - 11/14 (78.6%) HSCT - 10/14 (71.4%) busulfan - 9/14 (64.3%) melphalan - 13/14 (92.9%) cyclophosphamide - 1/14 (7.1%) thiotepa - 5/8 (%) of girls HRT (1 unknown, 2 started after development of FNH) - 10/14 (71.4%) previous SOS <u>Natural course</u> - 4/14 (28.6%) underwent biopsy - 9 patients had follow-up median 2.5 (range 1-10.5) yr; 5 patients did not have long-term follow-up - 13/14 (92.9%) alive at last follow-up - 1/14 (7.1%) died of a cause unrelated to FNH - 5/9 (55.6%) with radiological follow-up had an increase in the number of lesions - 0/9 (0%) with radiological follow-up had any sign of associated portal hypertension on Doppler ultrasound
Conclusions:	<u>Prevalence:</u> The reported prevalence of FNH ranged from 0.45%-12.3% among CCS that underwent abdominal imaging. <u>Detection:</u> 71%-100% was an incidental finding by routine follow-up imaging examination. 0%-21% was an incidental finding by imaging examination because of abdominal pain. <u>Risk factors (in multivariable analyses):</u> There is some suggestion that abdominal radiotherapy, HSCT, HRT, younger age at HSCT and chronic GVHD may increase the risk of FNH. <u>Natural course:</u> 93%-100% were alive at last follow-up; 2 died of a cause unrelated to FNH (of which 1 extensive GVHD). 18%-22% remained substantially unchanged after radiological follow-up ranging from 1-12 year. 8%-56% developed one or more additional lesions after radiological follow-up ranging from 1-12 year. 10%-42% had an increase in size of one or more lesions after radiological follow-up ranging from 1-12 year. 0% showed malignant transformation after radiological follow-up ranging from 1-12 year.	

Note: The reported prevalences are biased due to the fact that FNH is only detected in patients undergoing imaging.

* Considerable overlap in included patients, at least 8 FNH cases.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase, FNH, focal nodular hyperplasia; gGT, gamma-glutamyltransferase; GVHD, graft-versus-host disease; HR, hazard ratio; HRT, hormone replacement therapy; HSCT, hematopoietic stem cell transplantation; OR, odds ratio; SOS, sinusoidal obstructive syndrome; TBI, total body irradiation.

Outcome	Study	No. and type of participants	Follow-up and age (median/mean, range) yr	Outcomes
25b. Incidence and natural course nodular regenerative hyperplasia n=2 studies	Brisse 2000	Total cohort of childhood cancer survivors not reported (only solid tumors); 9 NRH cases described	Interval between primary cancer treatment and NRH diagnosis: Mean 6.2 (range 1.3-15.6) yr Age at NRH diagnosis: Not reported	Detection of NRH - 9/9 (100%) routine imaging examination - 8/9 (88.9%) had no evidence of malignancy at diagnosis (1 had lung metastasis) - 8/9 (88.9%) multiple lesions Etiologic factors - 6/9 (66.7%) abdominal radiotherapy - 6/9 (66.7%) HSCT (most probably autologous, but not reported) - 9/9 (100%) chemotherapy - 4/9 (44.4%) SOS Natural course - 2/9 (22.2%) underwent biopsy - 8/9 (88.9%) alive at last follow-up (mean 1.6 years; 0.2-4 years) - 1/9 (11.1%) died of infection
	Yoo 2012	Total cohort of childhood cancer survivors not reported (only solid tumors); 15 NRH cases described	Interval between primary cancer treatment and NRH diagnosis: Median 8.5 (range 4.5-13.5) yr Age at NRH diagnosis: Median 12.7 (range 8-20) yr	Detection of NRH - 15/15 (100%) routine imaging examination - 2/15 (13.3%) elevated ALT and AST - 9/15 (60.0%) multiple lesions Etiologic factors - 13/15 (87.7%) radiation involving the abdomen (TBI (n=10), TBI and local radiotherapy (n=4), local radiotherapy alone (n=1)) - 12/15 (80.0%) HSCT (majority autologous) - 12/15 (80.0%) high-dose chemotherapy - 4/15 (26.7%) history of SOS - 0/15 (0%) GVHD - 1/15 (6.7%) hepatitis B positive Natural course - 4/15 (26.7%) underwent biopsy - 1/15 (6.7%) FNH detected by biopsy
Conclusions:	Detection: 100% was an incidental finding by routine imaging examination. Natural course:			

	89% were alive at last follow-up; 1 died of infection.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase, FNH, focal nodular hyperplasia; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; NRH, nodular regenerative hyperplasia; SOS, sinusoidal obstructive syndrome; TBI, total body irradiation.