Summary of findings tables, grading of the evidence and detailed conclusions of evidence pulmonary dysfunction surveillance

PICO 1: Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Allogeneic HSCT n (%)	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
1 What is the risk of <u>obstructive</u> abnormalities in CAYA survivors treated with allogeneic HSCT compared to CAYA not treated with HSCT?	Record 2016 (1)	143 CCS	Mean 14.1 ± 4.8 (SD)	67 (46.9%)	Obstructive (FVC, FEV1, FEV1/FVC <80%pred or FEF25–75% <68%) 30% (20/67) HSCT 22% (17/76) no HSCT	Univariable comparison Chi2 HSCT Yes/No 0.30	1. No 2. Yes Wang X, Pediatr Pulmonol 2005; Hankinson JL, Am J Respir Crit Care Med 1999 3. No 4. Yes 5. No 6. Yes	Retrospective cohort SB: high risk AB: low risk DB: low risk CF: high risk

GRADE assessment:		
<u>Study design:</u>	+4	Retrospective cohort study
<u>Study limitations:</u>	-2	Some limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding high in 1/1
<u>Consistency:</u>	0	One study only
<u>Directness:</u>	-1	Results are direct, population and outcomes broadly generalizable; PFT quality unsure (no control group mentioned, no quality checks performed, no cleaning of lung function data described)
<u>Precision:</u>	-2	One study only, univariable comparison and no effect measure
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	0	No effect measure, only univariable comparison
<u>Dose-response:</u>	0	Not applicable
<u>Plausible confounding:</u>	0	Only univariable comparison
Quality of evidence:	⊕⊖⊖⊖ VERY LOW	
Conclusion:	No significant effect on obstructive abnormalities (FEV1, FEV1/FVC <80%pred or FEF25–75% <68%) in CAYA cancer survivors after allogeneic HSCT vs. no allogeneic HSCT. (1 study; 1 non-significant effect; 143 participants; 37 obstructive)	
Comment:	Only univariable comparison between CCS exposed to allogeneic HSCT and not exposed with Chi2 test and no effect measure.	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Allogeneic HSCT n (%)	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
1 What is the risk of <u>restrictive</u> abnormalities in CAYA survivors treated with allogeneic HSCT compared to CAYA not treated with HSCT?	Record 2016 (1)	143 CCS	Mean 14.1 ± 4.8 (SD)	67 (46.9%)	Restrictive (TLC<80% pred) 13% (9/67) HSCT 13% (10/76) no HSCT	Univariable comparison Chi2 HSCT Yes/No 0.96	1. No 2. Yes Wang X, Pediatr Pulmonol 2005; Hankinson JL, Am J Respir Crit Care Med 1999 3. No 4. Yes 5. No 6. Yes	Retrospective cohort SB: high risk AB: low risk DB: low risk CF: high risk

GRADE assessment:		
<u>Study design:</u>	+4	Retrospective cohort study
<u>Study limitations:</u>	-2	Some limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding high in 1/1
<u>Consistency:</u>	0	One study only
<u>Directness:</u>	-1	Results are direct, population and outcomes broadly generalizable; PFT quality unsure (no control group mentioned, no quality checks performed, no cleaning of lung function data described)
<u>Precision:</u>	-2	One study only, univariable comparison and no effect measure
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	0	No effect measure, only univariable comparison
<u>Dose-response:</u>	0	Not applicable
<u>Plausible confounding:</u>	0	Only univariable comparison
Quality of evidence:	⊕⊖⊖⊖ VERY LOW	
Conclusion:	No significant effect on restrictive abnormalities (TLC<80% pred) in CAYA cancer survivors after allogeneic HSCT vs. no allogeneic HSCT. (1 study; 1 non-significant effect ; 143 participants; 19 restrictive)	
Comment:	Only univariable comparison between CCS exposed to allogeneic HSCT and not exposed with Chi2 test and no effect measure.	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Allogeneic HSCT n (%)	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
1 What is the risk of <u>hyperinflation</u> in CAYA survivors treated with allogeneic HSCT compared to CAYA not treated with HSCT?	Record 2016 (1)	143 CCS	Mean 14.1 ± 4.8 (SD)	67 (46.9%)	Hyperinflation (RV >120%pred or RV/TLC >28%pred) 52% (35/67) HSCT 32% (24/76) no HSCT	Univariable comparison Chi2 HSCT Yes/No 0.01	1. No 2. Yes Wang X, Pediatr Pulmonol 2005; Hankinson JL, Am J Respir Crit Care Med 1999 3. No 4. Yes 5. No 6. Yes	Retrospective cohort SB: high risk AB: low risk DB: low risk CF: high risk

GRADE assessment:		
<u>Study design:</u>	+4	Retrospective cohort study
<u>Study limitations:</u>	-2	Some limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding high in 1/1
<u>Consistency:</u>	0	One study only
<u>Directness:</u>	-1	Results are direct, population and outcomes broadly generalizable; PFT quality unsure (no control group mentioned, no quality checks performed, no cleaning of lung function data described)
<u>Precision:</u>	-2	One study only, univariable comparison and no effect measure
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	0	No effect measure, only univariable comparison
<u>Dose-response:</u>	0	Not applicable
<u>Plausible confounding:</u>	0	Only univariable comparison
Quality of evidence:	⊕⊖⊖⊖ VERY LOW	
Conclusion:	Increased risk for hyperinflation (RV >120%pred or RV/TLC >28%pred) in CAYA cancer survivors after allogeneic HSCT vs. no allogeneic HSCT (1 study; 1 significant effect; 143 participants; 59 hyperinflation)	
Comment:	Only univariable comparison between CCS exposed to allogeneic HSCT and not exposed with Chi2 test and no effect measure.	

1a Age at hematopoietic stem cell transplantation (HSCT)

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Allogeneic HSCT n (%)	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
1a What is the risk of <u>obstructive</u> abnormalities in younger compared to older age at HSCT?	Inaba 2010 (2)	89 CSS with hematological disease	Median 8.9 (range 1.7-16.4)	89 (100%)	% of CCS below predicted values for $FEF_{25\%-75\%}$ 49% $FEF_{25\%-75\%}$ (<67%pred)	Hazard Ratio (p-value) Older age at HSCT continuously, per year 1.082 (0.038)	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999 3. No 4. Yes: ATS 5. No 6. No	Prospective cohort SB: High risk AB: Low risk DB: Low risk CF: Unclear
	Ginsberg, 2010 (3)	317 CCS (PFT post HSCT) 133 CCS (PFT pre and post HSCT)	0 - >5 years	241 (76%) Age at HSCT: a. <7.8 yr (n=77) b. 7.8 – 11.4 yr (n=79) c. 11.4-14.6 yr (n=79) d. >14.6 yr (n=79)	Z-score Mean (SD) for FEV1 at last post-transplant test a. -1.270 (1.495) b. -1.862 (1.469) c. -1.730 (1.800) d. -1.817 (1.936)	P-value of ANOVA 0.0790	1. No 2. Yes Rosenthal M, Thorax, 1993, Hankinson JL, Am J Respir Crit Care Med, 1999 3. No 4. Yes: ATS 5. No 6. No	Retrospective cohort SB: High risk AB: Low risk DB: Low risk CF: Unclear

GRADE assessment:		
<u>Study design:</u>	+4	1 prospective cohort study, 1 retrospective cohort study
<u>Study limitations:</u>	-1	Some limitations: Selection bias high in 2/2; Attrition bias low in 2/2; Detection bias low in 2/2; unclear in 2/2
<u>Consistency:</u>	0	No important inconsistency, both studies show increased risk with older age at HSCT, one p-value significant but hazard ration without confidence interval
<u>Directness:</u>	0	Results are direct, population and outcomes broadly generalizable; PFT quality good (2/2 stated reference values and 2/2 the use if ATS guidelines)
<u>Precision:</u>	-1	Precision cannot be judged as 1/2 show results with p-value only and 1/2 shows results with Hazard rate but without 95%CI
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	0	No large magnitude of effect
<u>Dose-response:</u>	0	No clear age response relationship
<u>Plausible confounding:</u>	0	No plausible confounding
Quality of evidence:	⊕⊕⊖⊖ LOW	
Conclusion:	Increased risk for obstructive abnormalities ($FEF_{25\%-75\%}$) in CAYA cancer survivors older vs. younger at allogeneic HSCT. (2 studies; 1 significant effect [$FEF_{25\%-75\%}$], 1 non-significant effect [FEV1]; 406 participants)	
Comment:	Only univariable comparison between CCS older vs. younger at allogeneic HSCT and effect measure in one study only.	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Allogeneic HSCT n (%)	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
1a What is the risk of <u>restrictive</u> abnormalities in	Ginsberg, 2010 (3)	317 CCS (PFT post HSCT)	0 - >5 years	241 (76%)	Z-score Mean (SD) at last post-transplant test **FVC**	P-value of ANOVA 0.0263	1. No 2. Yes	Retrospective cohort SB: High risk AB: Low risk

younger compared to older age at HSCT?		133 CCS (PFT pre and post HSCT)		Age at transplant categorized: a. <7.8 yr (n=77) b. 7.8 – 11.4 yr (n=79) c. 11.4-14.6 yr (n=79) d. >14.6 yr (n=79)	a. -1.202 (1.234) b. -1.707 (1.410) c. -1.720 (1.668) d. -17.796 (1.770) **TLC** a. - 0.587 (1.709) b. - 1.041 (1.248) c. - 0.812 (1.411) d. - 0.836 (1.197)	0.4319	Rosenthal M, Thorax, 1993, Hankinson JL, Am J Respir Crit Care Med, 1999 3. No 4. Yes: ATS 5. No 6. No	DB: Low risk CF: Unclear
	Wieringa 2005 (4)	39 CSS with hematological disease	Median 4.5 years	39 (100%) Age at HSCT >10yr vs. <10yr	 Higher **TLC** when older at HSCT *(no numbers stated)*	P-value from Student paired t-test, >10yr vs. <10yr 0.08	1. Yes 2. Yes Polgar G, Rev Resp Dis, 1979 3. No 4. No 5. No 6. No	Retrospective cohort SB: High risk AB: Low risk DB: Low risk CF: High risk

GRADE assessment:		
Study design:	+4	2 retrospective cohort studies
Study limitations:	-2	Some limitations: Selection bias high in 2/2; Attrition bias low in 2/2; Detection bias low in 2/2; Confounding high in 1/2, unclear in 1/2
Consistency:	0	No important inconsistency. No significant effect on TLC in 2 studes and significant effect on FVC in 1 study
Directness:	-1	Population and outcomes broadly generalizable; PFT quality unsure (2/2 stated reference values and 1/2 the use if ATS guidelines)
Precision:	-1	Precision cannot be judged as 2/2 show results with p-value only
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No clear age response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:	⊕⊖⊖⊖ VERY LOW	
Conclusion:	Inconsistent findings for restrictive abnormalities (TLC) in CAYA cancer survivors older vs. younger at allogeneic HSCT. (2 studies; 1 significant effect [FVC], 2 non-significant effects [TLC]; 356 participants)	
Comment:	Only univariable comparison between CCS older vs. younger at allogeneic HSCT and no effect measure	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Allogeneic HSCT n (%)	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
1a What is the risk of <u>hyperinflation</u> in younger compared to older age at HSCT?								
No study								

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Allogeneic HSCT n (%)	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
1a What is the risk of <u>diffusion capacity impairment</u> in younger compared to older age at treatment?	Inaba 2010 (2)	89 CSS with hematological disease	Median 8.9 (range 1.7-16.4)	89 (100%)	% of CCS below predicted values for $DLCO_{corr}$ 64% $DLCO_{corr}$ (<80%pred)	Hazard Ratio (p-value) Older age at HSCT continuously, per year 1.102 (0.005)	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999 3. No 4. Yes: ATS 5. No 6. No	Prospective cohort SB: High risk AB: Low risk DB: Low risk CF: Unclear
	Ginsberg, 2010 (3)	317 CCS (PFT post HSCT) 133 CCS (PFT pre and post HSCT)	0 - >5 years	241 (76%) Age at HSCT: a. <7.8 yr (n=77) b. 7.8 – 11.4 yr (n=79) c. 11.4-14.6 yr (n=79) d. >14.6 yr (n=79)	Z-score Mean (SD) for DLCO at last post-transplant test a. -1.649 (1.830) b. -1.889 (1.531) c. -1.791 (1.665) d. -2.182 (1.341)	P-value of ANOVA 0.432	1. No 2. Yes Rosenthal M, Thorax, 1993, Hankinson JL, Am J Respir Crit Care Med, 1999 3. No 4. Yes: ATS 5. No 6. No	Retrospective cohort SB: High risk AB: Low risk DB: Low risk CF: Unclear
	Leung 2007 (5)	155 CCS	Median 9 (range 3.1-15.9)	155 (100%)	35% DLCO (<80%pred)	Hazard Ratio (95%CI) Older age at HSCT continuously, per year 1.1 (1.04-1.17)	1. No 2. No 3. No 4. No 5. No 6. No	Prospective cohort SB: Low risk AB: Low risk DB: Low risk CF: Low risk

GRADE assessment:		
<u>Study design:</u>	+4	2 prospective cohort studies, 1 retrospective cohort study
<u>Study limitations:</u>	-1	Some limitations: Selection bias high in 2/3, low in 1/3; Attrition bias low in 3/3; Detection bias low in 3/3; Confounding unclear in 2/3, low in 1/3
<u>Consistency:</u>	0	No important inconsistency, two studies show increased risk with older age at HSCT, 2/3 showed significant effect
<u>Directness:</u>	-1	Population and outcomes broadly generalizable; PFT quality unsure (not homogeneous across studies, 2/3 stated reference values and 2/3 the use if ATS guidelines)
<u>Precision:</u>	-1	Moderate imprecision, 1/3 show precise results with small confidence interval, in 2/3 precision cannot be judged results shown as p-value only
<u>Publication bias:</u>	0	Unlikely

Effect size:	0	No large magnitude of effect
Dose-response:	0	No clear age response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:	⊕⊖⊖⊖ VERY LOW	
Conclusion:	Increased risk for diffusion impairment (DLCO) in CAYA cancer survivors older vs. younger at allogeneic HSCT. (3 studies; 2 significant effects, 1 non-significant effect; 561 participants)	
Comment:	One study with high precision, in two studies precision cannot be judged	

1b Chronic Graft versus Host Disease (cGvHD)

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Allogeneic HSCT	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
1b What is the risk of <u>obstructive</u> abnormalities in patients with cGvHD compared to patients without cGvHD?	Madanat-Harjuoja, 2014 (6)	51 CSS with hematological disease	Median 4.1 years Chronic GvHD: - 55% No - 22% limited - 23% extensive Acute GvHD: - 43% No/Grade I - 57% Grade II-IV	51 (100%) Anlyses: a. No vs limited cGvHD b. No vs extensive cGvHD c. No/Grade I vs Grade II-IV aGvHD	FEV1 FEV1/FVC	Random effect modeling for longitudinal analysis (estimates of coefficient, p-value) a: 8.0871 (0.314) b: - 27.8368 (0.003) c:- 13.8726 (0.015) a: 0.0292 (0.582) b:- 0.1366 (0.026) c: - 0.0081 (0.830)	1. No 2. Yes Quanjer PH, Eur Respir J Suppl,, 1997 3. Yes 4. Yes: ATS 5. Yes 6. No	Retrospective cohort SB: High risk AB: Low risk DB: Low risk CF: Low risk
	Hoffmeister, 2006 (7)	215 CSS with hematological disease	Median 10.5 (range 5-27.5)	202 (94%) cGvHD: Yes: n=71 No: n=144	Total 26 **Obstructive** FEv1/FVC<80%, FEV1<100%pred 20% with cGvHD 8% without GvHD	Odds Ratio (95%CI) cGVHD yes/no Multivariable analysis 4.4 (1.6-12)	1. No 2. Yes Rosenthal M, Thorax, 1993; Crapo RO, Am Rev Respir Dis, 1981; Crapo RO, Bulletin Europeen de Physiopathologie Respiratoire, 1982 3. No 4. Yes: ATS 5. No 6. No	Retrospective cross-sectional SB: High risk AB: Low risk DB: Low risk CF: High risk

GRADE assessment:		
<u>Study design:</u>	+4	1 retrospective cohort study, 1 retrospective cross-sectional study
<u>Study limitations:</u>	-2	Some limitations: Selection bias high in 2/2; Attrition bias low in 2/2; Detection bias low in 2/2; Confounding high in 1/2, low in 1/2
<u>Consistency:</u>	0	No important inconsistency; both studies show increased risk of obstructive abnormalities with development of cGvHD; one study showed significant effect of aGvHD on obstructive abnormalities
<u>Directness:</u>	0	Population and outcomes broadly generalizable; PFT quality good (2/2 stated reference values and 2/2 the use if ATS guidelines)
<u>Precision:</u>	-1	Important imprecision, 1/2 with results from multivariable analysis but with large confidence interval, 1/2 precision cannot be judged as results shown as p-value only

Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:	⊕⊖⊖⊖ VERY LOW	
Conclusion:	Increased risk for obstructive abnormalities (FEV1, FEV1/FVC) in CAYA cancer survivors after chronic GvHD vs. no GvHD, especially extensive cGvHD. Increased risk for obstructive abnormalities (FEV1, FEV1/FVC) in CAYA cancer survivors after acute GvHD Grade II-IV vs. no GvHD/Grade I (onse study). (2 studies; 2 significant effects, 266 participants)	
Comments:	Two studies with important imprecision	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Allogeneic HSCT	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
1b What is the risk of <u>restrictive</u> abnormalities in patients with cGvHD compared to patients without cGvHD?	Madanat-Harjuoja, 2014 (6)	51 CSS with hematological disease	Median 4.1 years Chronic GvHD: - 55% No - 22% limited - 23% extensive Acute GvHD: - 43% No/Grade I - 57% Grade II-IV	51 (100%) Anlyses performed: a. No vs limited cGvHD b. No vs extensive cGvHD c. No/Grade I vs Grade II-IV aGvHD	**FVC**	Random effect modeling for longitudinal analysis (estimates of coefficient, p-value) a: 7.5973 (0.243) b: - 18.90747 (0.012) c: - 13.1761 (0.004)	1. No 2. Yes Quanjer PH, Eur Respir J Suppl,, 1997 3. Yes 4. Yes: ATS 5. Yes 6. No	Retrospective cohort SB: High risk AB: Low risk DB: Low risk CF: Low risk

GRADE assessment:		
<u>Study design:</u>	+4	1 retrospective cohort study
<u>Study limitations:</u>	-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
<u>Consistency:</u>	0	One study only
<u>Directness:</u>	0	Population and outcomes broadly generalizable; PFT quality good (2/2 stated reference values and 2/2 the use if ATS guidelines)
<u>Precision:</u>	-1	Some imprecision, only 1 study, no effect size not shown
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	0	No large magnitude of effect
<u>Dose-response:</u>	0	Not applicable
<u>Plausible confounding:</u>	0	No plausible confounding
Quality of evidence:	⊕⊖⊖⊖ VERY LOW	
Conclusion:	Increased risk of restrictive abnormalities (FVC) in CAYA cancer survivors after extensive chronic GvHD and acute GvHD Grade II-IV vs. no GvHD. (1 study; 1 significant effect; 51 participants)	
Comments:	One study only with some limitations	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Allogeneic HSCT	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
1b What is the risk of <u>diffusion capacity impairment</u> in patients with cGvHD compared to patients without cGvHD?	Leung 2007 (5)	155 CCS	Median 9 (range 3.1-15.9)	155 (100%) cGvHD (26%) No cGvHD (74%)	 34% DLCO (<80%pred)	Hazard Ratio (95%CI) 1.96 (1.12-3.44)	1. No 2. No 3. No 4. No 5. No 6. No	Prospective cohort SB: Low risk AB: Low risk DB: Low risk CF: Low risk

GRADE assessment:		
<u>Study design:</u>	+4	1 prospective cohort study
<u>Study limitations:</u>	0	No limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding low in 1/1
<u>Consistency:</u>	NA	One study only
<u>Directness:</u>	-1	No statement on generalizability possible (no reference values and no use of ATS guidelines stated)
<u>Precision:</u>	-1	Some imprecision, only 1 study but precise results with small confidence interval
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	0	No large magnitude of effect
<u>Dose-response:</u>	0	Not applicable
<u>Plausible confounding:</u>	0	No plausible confounding
Quality of evidence:	⊕⊕⊖⊖ LOW	
Conclusion:	Increased risk for diffusion capacity impairment (DLCO) in CAYA cancer survivors with chronic GvHD vs. no cGvHD. (1 study; 1 significant effect, 155 participants)	
Comments:	One study only with some limitations	

1c Infection during hematopoietic stem cell transplantation

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Allogeneic HSCT	Pulmonary function Outcomes	Effect size	Risk of bias
1c What is the risk in patients who had a pulmonary infection during HSCT compared to patients without pulmonary infection during HSCT?							

No study

1d Total body irradiation (TBI) as conditioning for hematopoietic stem cell transplantation (HSCT)

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Allogeneic HSCT N (%)	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
1d What is the risk of <u>obstructive</u> abnormalities for patients treated with total body irradiation as conditioning for HSCT?	Leung 2007 (5)	155 CCS	Median 9 (range 3.1-15.9)	Allogeneic: 155 (100%) TBI: 123 (85%)	Number of CCS with respective parameter below predicted values 41 FEV1/FVC (<85%pred)	Hazard Ratio (95%CI) 2.39 (1.10-5.74)	1. No 2. No 3. No 4. No 5. No 6. No	Prospective cohort SB: Low risk AB: Low risk DB: Low risk CF: Low risk
	Hoffmeister, 2006 (7)	215 CSS with hematological disease	Median 10.5 (range 5-27.5) No TBI: n=53 FTBI: n=133 1.2Gy: n=37 >1.2Gy: n=96 SFTBI: n=29	Allogeneic: 202 (94%) Analyses performed: a. No TBI vs FTBI 1.2Gy b. No TBI vs FTBI 2.0-2.25 Gy c. No TBI vs SFTBI	Total 26 obstructive FEv1/FVC<80%, FEV1<100%pred 3% (1/37): FTBI 1.2Gy 13% (12/96): FTBI 2.0-2.25Gy 7% (2/29): SFTBI	Multivariate Analysis Odds Ratio (95%CI) a. 0.1 (0.0-1.4) b. 0.9 (0.3-2.8) c. 0.1 (0.0-0.5)	1. No 2. Yes: Rosenthal M, Thorax, 1993; Crapo RO, Am Rev Respir Dis, 1981; Crapo RO, Bulletin Europeen de Physiopathologie Respiratoire, 1982 3. No 4. Yes: ATS 5. No 6. No	Retrospective cross-sectional SB: High risk AB: Low risk DB: Low risk CF: High risk

GRADE assessment:		
<u>Study design:</u>	+4	1 prospective cohort study, 1 retrospective cross-sectional study
<u>Study limitations:</u>	-2	Some limitations: Selection bias high in 1/2, low in 1/2; Attrition bias low in 2/2; Detection bias low in 2/2; Confounding high in 1/2, low in 1/2
<u>Consistency:</u>	0	No important inconsistency. One study reports significant reduction in FEV1/FVC in CCS exposed to TBI. One study compares different TBI regimens to non-TBI with no significant association.
<u>Directness:</u>	-1	Population and outcomes broadly generalizable; PFT quality unsure (not homogeneous, 1/2 stated reference values and 1/2 the use if ATS guidelines)
<u>Precision:</u>	0	No imprecision, 2/2 show precise results with small confidence interval.
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	1	Large magnitude of effect in one study
<u>Dose-response:</u>	0	Not applicable
<u>Plausible confounding:</u>	0	No plausible confounding
Quality of evidence:	⊕⊖⊖⊖ VERY LOW	
Conclusion:	Inconsistent findings. Increased risk of obstructive abnormalities (FEV1/FVC) in CAYA cancer survivors after TBI vs. no TBI (one study only, fractioning not mentioned). No significant effect of different fractioning (one study). (2 studies; 2 significant effect [TBI yes/no], 1 non-significant effect [different fractioning of TBI]; 370 participants)	
Comments:	Two studies with some limitations but high precision	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Allogeneic HSCT N (%)	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
1d What is the risk of <u>restrictive</u> abnormalities for patients treated with total body irradiation as conditioning for HSCT?	Leung 2007 (5)	155 CCS	Median 9 (range 3.1-15.9)	Allogeneic: 155 (100%) TBI: 123 (85%)	Number of CCS with respective parameter below predicted values 48 **TLC** (<80%pred)	Hazard Ratio (95%CI) 2.26 (1.04-4.95)	1. No 2. No 3. No 4. No 5. No 6. No	Prospective cohort SB: Low risk AB: Low risk DB: Low risk CF: Low risk
	Hoffmeister, 2006 (7)	215 CSS with hematological disease	Median 10.5 (range 5-27.5) No TBI: n=53 FTBI: n=133 1.2Gy: n=37 >1.2Gy: n=96 SFTBI: n=29	Allogeneic: 202 (94%) Analyses performed: a. No TBI vs FTBI 1.2Gy b. No TBI vs FTBI 2.0-2.25 Gy c. No TBI vs SFTBI	Total 67 **restrictive** TLC <80%pred 19% (7/37) when FTBI 1.2Gy 31% (30/96) when FTBI 2.0-2.25Gy 72% (21/29) when SFTBI	Multivariate Analysis Odds Ratio (95%CI) a. 2.5 (0.4-16) b. 2.8 (0.6-13) c. 22.0 (3.9-120)	1. No 2. Yes: Rosenthal M, Thorax, 1993; Crapo RO, Am Rev Respir Dis, 1981; Crapo RO, Bulletin Europeen de Physiopathologie Respiratoire, 1982 3. No 4. Yes: ATS 5. No 6. No	Retrospective cross-sectional SB: High risk AB: Low risk DB: Low risk CF: High risk

GRADE assessment:		
<u>Study design:</u>	+4	1 prospective cohort study, 1 retrospective cross-sectional study
<u>Study limitations:</u>	-2	Some limitations: Selection bias high in 1/2, low in 1/2; Attrition bias low in 2/2; Detection bias low in 2/2; Confounding high in 1/2, low in 1/2
<u>Consistency:</u>	0	No inconsistency, both studies report reduction in TLC in CAYA cancer survivors exposed to TBI.
<u>Directness:</u>	-1	Population and outcomes broadly generalizable; PFT quality unsure (1/2 stated reference values and 1/2 the use if ATS guidelines)
<u>Precision:</u>	-1	Important imprecision, both studies show precise results, but the 95%CI but is large in one study
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	1	Large magnitude of effect on one study
<u>Dose-response:</u>	0	Not applicable
<u>Plausible confounding:</u>	0	No plausible confounding
Quality of evidence:	⊕⊖⊖⊖ VERY LOW	
Conclusion:	Increased risk for restrictive abnormalities (TLC) in CAYA cancer survivors after TBI as conditioning for HSCT vs. no TBI. No significant effect of different fractioning (one study). (2 studies; 2 significant effects [TBI yes/no], 1 non-significant effect [different fractioning of TBI]; 370 participants)	
Comments:	Results of one study with large confidence intervals.	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Allogeneic HSCT N (%)	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
1d What is the risk of <u>diffusion capacity impairment</u> for patients treated with total body irradiation as conditioning for HSCT?	Leung 2007 (5)	155 CCS	Median 9 (range 3.1-15.9)	Allogeneic: 155 (100%) TBI: 123 (85%)	Number of CCS with respective parameter below predicted values 52/155 DLCO (<80%pred)	Hazard Ratio (95%CI) 2.24 (1.07-5.09)	1. No 2. No 3. No 4. No 5. No 6. No	Prospective cohort SB: Low risk AB: Low risk DB: Low risk CF: Low risk
GRADE assessment:								
<u>Study design:</u>	+4	1 prospective cohort study						
<u>Study limitations:</u>	0	No limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding low in 1/1						
<u>Consistency:</u>	NA	One study only						
<u>Directness:</u>	-1	No information on generalizability; PFT quality unsure (no reference values and no information on guidelines stated)						
<u>Precision:</u>	-1	Some imprecision, only 1 study but precise results with small confidence interval						
<u>Publication bias:</u>	0	Unlikely						
<u>Effect size:</u>	1	Large magnitude of effect						
<u>Dose-response:</u>	0	Not applicable						
<u>Plausible confounding:</u>	0	No plausible confounding						
Quality of evidence:	⊕⊕⊕⊖ MODERATE							
Conclusion:	Increased risk for diffusion capacity impairment (DLCO) in CAYA cancer survivors after TBI as conditioning for HSCT vs. no TBI. (1 study; 1 significant effect, 155 participants)							
Comments:	One study with high precision							

PICO 2: Cyclophosphamide (CYC)

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cyclophosphamide (CYC)	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
2 What is the risk of <u>obstructive</u> abnormalities in CAYA treated with CYC compared to CAYA not treated with CYC?	Jenney 1995 (8)	70 leukemia CCS	Median 4.2 (range 0.6-18.5)	Proportion receiving CYC unclear	Number of CCS with FEV1 below predicted values 36/69 FEV1 (<85% pred) 23/69 FEV1 (<80% pred)	p-value CYC yes vs no p<0.001	1. Yes 2. No 3. No 4. No 5. No 6. No	Prospective cross-sectional SB: high risk AB: low risk DB: unclear CF: unclear

GRADE assessment:		
<u>Study design:</u>	+4	1 retrospective cross-sectional study
<u>Study limitations:</u>	-2	Some limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding unclear in 1/1
<u>Consistency:</u>	NA	One study only
<u>Directness:</u>	-1	Population and outcomes broadly generalizable; PFT quality unsure (no reference values and guidelines stated)
<u>Precision:</u>	-1	Important imprecision, precision cannot be judged as 1/1 shows p-value only
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	0	No large magnitude of effect
<u>Dose-response:</u>	NA	Not applicable
<u>Plausible confounding:</u>	0	No plausible confounding
Quality of evidence:	⊕⊖⊖⊖ VERY LOW	
Conclusion:	Increased risk for obstructive abnormalities (FEV1) in CAYA cancer survivors after cyclophosphamide vs. no cyclophosphamide (1 study; 1 significant effect; 70 participants)	
Comments:	One study and precision cannot be judged as result is shown as p-value only	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cyclophosphamide (CYC)	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
2 What is the risk of <u>restrictive</u> abnormalities in CAYA treated with CYC compared to CAYA not treated with CYC?	Jenney 1995 (8)	70 leukemia CCS	Median 4.2 (range 0.6-18.5)	Proportion receiving CYC unclear	Number of CCS with respective parameter below predicted values 32/69 FVC (<85% pred) 20/69 FVC (<80% pred) 26/69 TLC (<85% pred) 20/69 TLC (<80% pred)	CYC leads to reduction in FVC, and TLC: p<0.001 p<0.001	1. Yes 2. No 3. No 4. No 5. No 6. No	Prospective cross-sectional SB: high risk AB: low risk DB: unclear CF: unclear
	Mulder 2011 (9)	193 CCS	Median 17.9 (range 5.6-36.8)	High-dose CYC 43 (22.3%)	34/193 Restrictive disease (TLC or FVC <75% pred)	Odds Ratio (95%CI) High-dose CYC vs no 2.15 (0.80-5.79)	1. No 2. No 3. No 4. No 5. No 6. No	Retrospective cohort SB: Low risk AB: Low risk DB: Low risk CF: Low risk

GRADE assessment:

Study design:	+4	1 retrospective cohort study, 1 prospective cross-sectional study
Study limitations:	-2	Some limitations: Selection bias high in 1/2, low in 1/2; Attrition bias low in 2/2; Detection bias low in 1/2, unclear 1/2; Confounding low in 1/2, unclear 1/2
Consistency:	0	No inconsistency. Both studies show more restrictive abnormalities in CCS exposed to CYC, but in one study this effect was not significant
Directness:	-1	Population and outcomes broadly generalizable; PFT quality unsure (both studies do not report reference values and guidelines used)
Precision:	-1	Important imprecision, 1/2 show precise results with small confidence interval, in 1/2 precision cannot be judged as p-value is shown only
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		Increased risk for restrictive abnormalities (FVC, TLC) in CAYA cancer survivors after cyclophosphamide vs. no cyclophosphamide (2 studies; 1 significant effects [FVC, TLC], 1 non-significant effects [FVC]; 263 participants)
Comments:		One study shows significant p-value only, one study shows effect measure by OR but with non-significant 95%CI.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cyclophosphamide (CYC)	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
2 What is the risk of diffusion capacity impairment in CAYA treated with CYC compared to CAYA not treated with CYC?	Mulder 2011 (9)	193 CCS	Median 17.9 (range 5.6-36.8)	High-dose CYC 43 (22.3%)	85/193 Diffusion impairment (DLCO <75% pred)	Odds Ratio (95%CI) High-dose CYC vs no 1.25 (0.58-2.71)	1. No 2. No 3. No 4. No 5. No 6. No	Retrospective cohort SB: Low risk AB: Low risk DB: Low risk CF: Low risk

GRADE assessment:		
Study design:	+4	1 retrospective cohort study
Study limitations:	0	No limitations: Selection low in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding low in 1/1
Consistency:	0	One study only
Directness:	-1	Population and outcomes broadly generalizable; PFT quality unsure (no reference values and use of guidelines stated)
Precision:	-1	Some imprecision, only 1 study but with precise results with small confidence interval
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant effect on diffusion capacity impairment (DLCO) in CAYA cancer survivors after cyclophosphamide vs. no cyclophosphamide. (1 study; 1 non-significant effect; 193 participants)
Comments:		One study only with non-significant 95%CI and no information on PFT quality.

2a Different doses

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cyclophosphamide	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias

2a What is the risk of <u>obstructive</u> abnormalities in CAYA survivors treated with different doses of CYC?	Green 2015 (10)	260 embryonal brain tumors	Minimum 2 yr	260 (100%)	Proportion of CCS with FEV1 below predicted after 60 months 29% **FEV1** (<80% pred)	CYC dose was not found to be a significant predictor of FEV1 % predicted. (univariable model)	1. No 2. Yes Newth CJ, Eur Respir J, 1997; Stocks J, Eur Respir J, 1995; Paoletti P, Am Rev Respir Dis, 1985; Hankinson JL, Am J Respir Crit Care Med, 1999; Wang X, Pediatr Pulmonol, 1993; Knudosn RJ, Am Rev Respir Dis, 1983; Eigen H, Am J Respir Crit Care Med, 2001; Polgar G, 1971; Kim YJ, Pediatr Pulmonol, 2012; Zapletal A, 1987; HIbbert ME, Pediatr Pulmonol, 1989; Stanojevic S, Am J Respir Crit Care Med, 2008 3. No 4. Yes: ATS 5. No 6. No	Prospective cohort SB: low risk AB: high risk DB: unclear CF: high risk

GRADE assessment:		
<u>Study design:</u>	+4	1 prospective cohort study
<u>Study limitations:</u>	-3	Severe limitations: Selection bias low in 1/1; Attrition bias high 1/1 ; Detection bias unclear 1/1; Confounding high in 1/1
<u>Consistency:</u>	0	One study only
<u>Directness:</u>	-1	Population and outcomes broadly generalizable; PFT quality unsure (10 different references stated und use of ATS guidelines)
<u>Precision:</u>	-2	Important imprecision, univariable analysis only, no effect size mentioned, one study only
<u>Publication bias:</u>	0	Publication bias unlikely
<u>Effect size:</u>	0	No large magnitude of effect
<u>Dose-response:</u>	0	No clear dose response relationship
<u>Plausible confounding:</u>	0	No plausible confounding
Quality of evidence:	⊕⊖⊖⊖ VERY LOW	
Conclusion:	No significant effect on obstructive abnormalities with increasing doses of cyclophosphamide (1 study; 260 participants)	
Comments:	One study only, univariable analysis, and no effect size mentioned or p-value.	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Cyclophosphamide	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
2a What is the risk of <u>restrictive</u> abnormalities in CAYA survivors	Nysom 1998 (11)	94 leukemia CCS	Median 10.6 (range 3.4-23.4)	43 (46%) Cumulative dose of CYC as continuous variable	17% (15/89) with reduced or raised **TLC**	Regression coefficient (95%CI), p-value: Simple regression -0.11 (-0.23 – 0.01), 0.07	1. No 2. Yes Reference form own laboratory by adjusting published reference values (Quanjer PH, Pediatr Pulmonol. 1995;	Retrospective cohort SB: High risk AB: Low risk DB: Unclear CF: High risk

treated with different doses of CYC?			Multiple regression: -0.14 (-0.25 – -0.02), 0.02	Rosenthal M, Thorax, 1993; Quanjer PH, Bull Eur Physiopathol Respir, 1983: Stam H, Pediatr Pulmonl, 1996) 3. No 4. Yes 5. No 6. Yes
GRADE assessment:				
Study design:	+4	1 retrospective cohort study		
Study limitations:	-2	Severe limitations: Selection bias high in 1/1; Attrition bias low in 1/1 ; Detection bias unclear 1/1; Confounding high in 1/1		
Consistency:	0	One study only		
Directness:	-1	Population and outcomes broadly generalizable; PFT quality good (reference values and ATS guidelines stated)		
Precision:	-1	Some imprecision, precise results with small confidence interval, only one study		
Publication bias:	-1	Publication bias likely, as not for all lung function parameters assessed the are shown (FEV1, FVC)		
Effect size:	0	No large magnitude of effect		
Dose-response:	1	Dose response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:	⊕⊖⊖⊖ VERY LOW			
Conclusion:	Increased risk for restrictive abnormalities (TLC) with increasing doses of cyclophosphamide in CAYA cancer survivors. (1 study; 89 participants with TLC measurements)			
Comments:	One study only with effect size and 95%CI mentioned.			

2b Age at exposure to cyclophosphamide

No study

PICO 3: Methotrexate (MTX)

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Methotrexate (MTX)	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
3 What is the risk of pulmonary dysfunction in CAYA treated with methotrexate compared to CAYA not treated with methotrexate?								

No study

3a Different doses

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Methotrexate (MTX)	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
3a What is the risk of obstructive abnormalities in CAYA survivors treated with different doses of MTX?								

No study

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Methotrexate (MTX)	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
3a What is the risk of <u>restrictive</u> abnormalities in CAYA survivors treated with different doses of MTX?	Nysom 1998 (11)	94 leukemia survivors	Median 10.6 (range 3.4-23.4)	16 (17%) with high-dose MTX (HDM) Number of HDM cycles (cont.)	17% (15/89) with reduced or raised **TLC**	Regression coefficient (95%CI), p-value: Simple regression: -0.005 (-0.08 - 0.07) 0.9	1. No 2. Yes Reference form own laboratory by adjusting published reference values (Quanjer PH, Pediatr Pulmonol. 1995; Rosenthal M, Thorax, 1993; Quanjer PH, Bull Eur Physiopathol Respir, 1983: Stam H, Pediatr Pulmonl, 1996) 3. No 4. Yes 5. No 6. Yes	Retrospective cohort SB: High risk AB: Low risk DB: Unclear CF: High risk

GRADE assessment:		
<u>Study design:</u>	+4	1 retrospective cohort study
<u>Study limitations:</u>	-2	Severe limitations: Selection bias high in 1/1; Attrition bias low in 1/1 ; Detection bias unclear 1/1; Confounding high in 1/1
<u>Consistency:</u>	0	One study only
<u>Directness:</u>	-1	Population and outcomes broadly generalizable; PFT quality unsure (“own” reference values generated but lung function procedure stated)
<u>Precision:</u>	-1	Some imprecision, precise results with small confidence interval, only one study
<u>Publication bias:</u>	-1	Publication bias likely, as not for all lung function parameters assessed the are shown (FEV1, FVC)
<u>Effect size:</u>	0	No large magnitude of effect
<u>Dose-response:</u>	0	No clear dose response relationship
<u>Plausible confounding:</u>	0	No plausible confounding
Quality of evidence:	⨁⊖⊖⊖ VERY LOW	
Conclusion:	No significant effect on restrictive abnormalities (TLC) after increasing doses of methotrexate in CAYA cancer survivors. (1 study; 89 with TLC measurements)	
Conclusion:	One study, small number of participants in whole study and only 16 exposed to high-dose methotrexate.	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Methotrexate (MTX)	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
3a What is the risk of <u>hyperinflation</u> in CAYA survivors treated with different doses of MTX?								

No study

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Methotrexate (MTX)	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
3a What is the risk of <u>diffusion</u> capacity impairment in CAYA survivors treated with different doses of MTX?								

No study

3b Age at exposure

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Methotrexate	Pulmonary function Outcomes	Effect size	Risk of bias
3b What is the risk in younger compared to older age at treatment?							

No study

PICO 4: Gemcitabine

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Methotrexate	Pulmonary function Outcomes	Effect size	Risk of bias
4 What is the risk of pulmonary dysfunction in CAYA treated with gemcitabine compared to CAYA not treated with gemcitabine?							

No study

PICO 5: Bleomycin

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Bleomycin exposure	Pulmonary function Outcomes	Effect size		Risk of bias
5 What is the risk of <u>obstructive</u> abnormalities in CAYA treated with bleomycin compared to CAYA not treated with bleomycin?	Record, 2016 (1)	143 CCS	Mean 14.1 ± 4.8 (SD)	48 (33.6%)	Obstructive (FEV1, FEV1/FVC <80% pred or FEF25–75% <68%) 12.5% (6/48) bleomycin 32.6% (31/95) no bleomycin	Univariable analysis comparing bleomycin yes/no (p-value) 0.01 **More in non-exposed**	1. No 2. Yes Wang X, Pediatr Pulmonol 2005; Hankinson JL, Am J Respir Crit Care Med 1999 3. No 4. Yes 5. No 6. Yes	Retrospective cohort SB: high risk AB: low risk DB: low risk CF: high risk
	De 2015 (12)	49 Osteosarcoma survivors	Median 2.91 (range 0.01-8.28)	38 (78%)	Proportion of CCS with abnormal results per lung function parameter in whole cohort 29% (14/49) FEV1 <80% pred 20% (10/49) FEF25–5% <68% pred 24% (12/49) Obstructive (FEV1/FVC <80%pred, FEV1<80%pred or FEF25-75<68%pred with normal TLC)	Univariable logistic regression comparing bleomycin yes/no Odds Ratio (p-value) 0.07 (<0.01) 0.18 (<0.05) 0.27 (NS) **More in non-exposed**	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Wang X, Pediatr Pulmonol, 1993 3. No 4. Yes: ATS 5. No 6. No	Retrospective cohort SB: High Risk AB: High Risk DB: Low risk CF: High Risk
	Denbo, 2014 (13)	21 Osteo-sarcoma survivor	Mean 20 yr (SD +/-9)	6 (28%)	Number of CCS with abnormal results per parameter	Univariable analysis comparing bleomycin yes/no	1. No 2. Yes	Prospective cohort SB: low risk AB: low risk

					(p-value) 1.00	Hankinson JL, Am J Respir Crit Care Med, 1999; Miller A, Am Rev Respir Dis, 1983 3. No 4. Yes: ATS, Morris AH, 1984 5. No 6. No	DB: unclear CF: high risk

GRADE assessment:		
Study design:	+4	2 retrospective cohort studies, 1 prospective cohort study
Study limitations:	-2	Severe limitations: Selection bias high in 2/1, low in 1/3; Attrition bias high in 1/3, low in 2/3 ; Detection bias low in 2/3, unclear in 1/3; Confounding high in 3/3
Consistency:	0	No inconsistency. All studies show no increased risk for obstructive abnormalities in CAYA survivors exposed to bleomycin.
Directness:	0	Population and outcomes broadly generalizable; PFT quality good (all studies mention reference values and lung function procedures)
Precision:	-1	Precision cannot be judged as 2/3 show p-value only and 1/3 shows OR but without 95%CI. All studies performed univariable analysis only.
Publication bias:	0	Publication bias unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Not applicable
Plausible confounding	0	No plausible confounding
Quality of evidence:	⊕⊖⊖⊖ VERY LOW	
Conclusion:	Deacreased risk for obstructive abnormalities (FEV1, FEF25-75, FEV1/FVC) after bleomycin vs. no bleomycin in CAYA cancer survivors. (3 studies; 2 significant effects, 1 non-significant effect; 213 participants)	
Comment:	All three studies with univariable analysis only and all report results with p-values only and without confidence intervals. Two studies with less than 50 participants.	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Bleomycin exposure	Pulmonary function Outcomes	Effect size		Risk of bias
5 What is the risk of restrictive abnormalities in CAYA treated with bleomycin compared to CAYA not treated with bleomycin?	Record, 2016 (1)	143 CCS	Mean 14.1 ± 4.8 (SD)	48 (33.6%)	Restrictive (TLC<80% pred) 12.5% (6/48) bleomycin 13.7% (13/95) no bleomycin	Univariable analysis comparing bleomycin yes/no (p-value) 0.84	1. No 2. Yes Wang X, Pediatr Pulmonol 2005; Hankinson JL, Am J Respir Crit Care Med 1999 3. No 4. Yes 5. No 6. Yes	Retrospective cohort SB: high risk AB: low risk DB: low risk CF: high risk

	Armenian 2015 (14)	121 CCS	Median 17.1 (6.3-40.1)	42 (34.7%)	Restrictive TLC <75%pred and FEV1 >80%pred) 19% (8/42) bleomycin 27% (21/79) no bleomycin	Univariable logistic regression Odds Ratio (95%CI) 0.7 (0.3-1.6)	1. Yes 2. No 3. No 4. Yes: ATS, Miller MR, Eur Respir J, 2005 5. No 6. Yes	Prospective cohort SB: Low risk AB: low risk DB: low risk CF: high risk
	De 2015 (12)	49 Osteo-sarcoma survivors	Median 2.91 (range 0.01-8.28)	38 (78%)	Proportion of CCS with abnormal results per lung function parameter in whole cohort 24% (12/49) FVC <80% pred 15% (7/49) TLC <77% pred 15% (7/49) Restrictive disease (TLC <77%)	Univariable logistic regression comparing bleomycin yes/no Odds Ratio (p-value) 0.15 (<0.05) 0.27 (NS) 0.27 (NS)	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Wang X, Pediatr Pulmonol, 1993 3. No 4. Yes: ATS 5. No 6. No	Retrospective cohort SB: High Risk AB: High Risk DB: Low risk CF: High Risk
	Denbo, 2014 (13)	21 Osteo-sarcoma survivor	Mean 20 yr (SD +/-9)	6 (28%)	Number of CCS with abnormal results per parameter FVC <80%predicted 50% (3/6) bleomycin 36% (5/14) no bleomycin TLC <75%predicted 17% (1/6) bleomycin 33% (7/15) no bleomycin	Univariate analysis comparing bleomycin yes/no (p-value) 0.642 0.623	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Miller A, Am Rev Respir Dis, 1983 3. No 4. Yes: ATS, Morris AH, 1984 5. No 6. No	Prospective cohort SB: low risk AB: low risk DB: unclear CF: high risk
	Mulder 2011 (9)	193 CCS	Median 17.9 (range 5.6-36.8)	110 (57%)	Total 34/193 Restrictive (TLC or FVC <75%)	Comparison of bleomycin yes/no Odds Ratio (95%CI) 1.5 (0.38-5.97)	1. No 2. No 3. No 4. No 5. No 6. No	Retrospective cohort SB: Low risk AB: Low risk DB: Low risk CF: Low risk

GRADE assessment:

Study design:	+4	3 retrospective cohort studies, 2 prospective cohort studies
Study limitations:	-3	Severe limitations: Selection bias high in 2/5, low in 3/5; Attrition bias high in 1/5, low in 4/5 ; Detection bias low in 4/5, unclear in 1/5; Confounding high in 4/5, low in 1/5
Consistency:	-1	Important inconsistency. Three studies show more restrictive abnormalities in CAYA survivors not exposed to bleomycin; in one study it depends on the outcome factor assessed whether exposed CAYA survivors are at risk or not (FVC vs TLC); in one study exposed CYAY survivors are more at risk than non-exposed.

Directness:	0	Population and outcomes broadly generalizable; PFT quality unsure (not homogeneous across studies, two studies do not mention reference values and one does not mention lung function procedures used)
Precision:	-1	Important imprecision, 2/5 shows precise results with small confidence interval, in 3/5 precision cannot be judged as results are shown with p-value only; 4/5 report univariable analysis only
Publication bias:	0	Publication bias unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Not applicable
Plausible confounding	0	No plausible confounding
Quality of evidence:	⊕⊖⊖⊖ VERY LOW	
Conclusion:	No significant effect on restrictive abnormalities (TLC or FVC) after bleomycin vs. no bleomycin in CAYA cancer survivors. (5 studies; 5 non-significant effects; 527 participants)	
Comment:	Four studies with univariable analysis only, three reported results with p-values only and without confidence intervals. Two studies with < 50 participants.	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Bleomycin exposure	Pulmonary function Outcomes	Effect size		Risk of bias
5 What is the risk of hyperinflation in CAYA treated with bleomycin compared to CAYA not treated with bleomycin?	Record, 2016 (1)	143 CCS	Mean 14.1 ± 4.8 (SD)	48 (33.6%)	Hyperinflation (RV >120%pred or RV/TLC >28%pred) 20.8% (10/48) with bleomycin 51.6% (49/95) without bleomycin	Univariable analysis comparing bleomycin yes/no (p-value) <0.01 **More in non-exposed**	1. No 2. Yes Wang X, Pediatr Pulmonol 2005; Hankinson JL, Am J Respir Crit Care Med 1999 3. No 4. Yes 5. No 6. Yes	Retrospective cohort SB: high risk AB: low risk DB: low risk CF: high risk
	De 2015 (12)	49 Osteo-sarcoma survivors	Median 2.91 (range 0.01-8.28)	38 (78%)	Proportion of CCS with abnormal RV/TLC in whole cohort 21% (10/49) RV/TLC >28%	Univariable logistic regression comparing bleomycin yes/no Odds Ratio (p-value) 0.15 (<0.05) **More in non-exposed**	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Wang X, Pediatr Pulmonol, 1993 3. No 4. Yes: ATS 5. No 6. No	Retrospective cohort SB: High Risk AB: High Risk DB: Low risk CF: High Risk

GRADE assessment:		
Study design:	+4	2 retrospective cohort studies
Study limitations:	-3	Severe limitations: Selection bias high in 2/2; Attrition bias high in 1/2, low in 1/2 ; Detection bias low in 2/2; Confounding high in 2/2
Consistency:	0	No inconsistency. Both studies show that hyperinflation is not associated with bleomycin exposure.
Directness:	0	Population and outcomes broadly generalizable; PFT quality good (both studies mention reference values and lung function procedures)
Precision:	-1	Precision cannot be judged as 2/2 show results with p-value only and 2/2 univariable analysis only
Publication bias:	0	Publication bias unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Not applicable

Plausible confounding	0	No plausible confounding
Quality of evidence:	⊕⊖⊖⊖ VERY LOW	
Conclusion:	Decreased risk for hyperinflation after bleomycin vs. no bleomycin in CAYA cancer survivors (2 studies with significant effect; 192 participants)	
Comment:	Both studies with univariable analysis and results as p-values only. One study with < 50 participants.	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Bleomycin exposure	Pulmonary function Outcomes	Effect size		Risk of bias
5 What is the risk of diffusion capacity impairment in CAYA treated with bleomycin compared to CAYA not treated with bleomycin?	Armenian 2015 (14)	121 CCS	Median 17.1 (6.3-40.1)	42 (34.7%)	Diffusion abnormality (DLCO <75%pred) 31% (13/42) bleomycin 37% (29/79) no bleomycin	Univariable logistic regression Odds Ratio (95%CI) 0.8 (0.4-1.7)	1. Yes 2. No 3. No 4. Yes: ATS, Miller MR, Eur Respir J, 2005 5. No 6. Yes	Prospective cohort SB: Low risk AB: low risk DB: low risk CF: high risk
	De 2015 (12)	49 Osteosarcoma survivors	Median 2.91 (range 0.01-8.28)	38 (78%)	9% (4/49) DLCO adj <65% pred 14% (6/49) Diffusion impairment (DLCO <65% or DLCOadj/VA <4ml(mmHg/min/l))	Univariable logistic regression comparing bleomycin yes/no Odds Ratio (p-value) 0.06 (<0.05) 0.08 (<0.01)	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Wang X, Pediatr Pulmonol, 1993 3. No 4. Yes: ATS 5. No 6. No	Retrospective cohort SB: High Risk AB: High Risk DB: Low risk CF: High Risk
	Denbo, 2014 (13)	21 Osteosarcoma survivor	Mean 20 yr (SD +/-9)	6 (28%)	Number of CCS with abnormal results per parameter $DLCO_{corr}$ <75%predicted 50% (3/6) bleomycin 46% (6/13) no bleomycin	Univariable analysis comparing bleomycin yes/no (p-value) 1.00	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Miller A, Am Rev Respir Dis, 1983 3. No 4. Yes: ATS, Morris AH, 1984 5. No 6. No	Prospective cohort SB: low risk AB: low risk DB: unclear CF: high risk
	Mulder 2011 (9)	193 CCS	Median 17.9 (range 5.6-36.8)	110 (57%)	Total 85/193 diffusion impairment (DLCO <75%)	Comparison of bleomycin yes/no Odds Ratio (95%CI) 1.99 (0.56-7.07)	1. No 2. No 3. No 4. No 5. No 6. No	Retrospective cohort SB: Low risk AB: Low risk DB: Low risk CF: Low risk

GRADE assessment:		
Study design:	+4	2 retrospective cohort studies, 2 prospective cohort studies
Study limitations:	-1	Severe limitations: Selection bias high in 1/4, low in 3/4; Attrition bias high in 1/4, low in 3/4 ; Detection bias low in 3/4, unclear in 1/4; Confounding high in 3/4, low in 1/4
Consistency:	-1	Important inconsistency. Two studies show higher DLCO impairment in CAYS survivors not exposed to bleomycin, one study shows no difference, and one study shows a not significant association between bleomycin exposure and diffusion capacity impairment
Directness:	-1	Population and outcomes broadly generalizable; PFT quality unsure (not homogeneous across studies, two studies do not mention reference values and one does not mention lung function procedures used)
Precision:	-1	Important imprecision, 2/4 shows precise results with small confidence interval, in 2/4 precision cannot be judged as results are shown as p-value only; 3/4 report univariable analysis only
Publication bias:	0	Publication bias unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Not applicable
Plausible confounding	0	No plausible confounding
Quality of evidence:	⊕⊖⊖⊖ VERY LOW	
Conclusion:	Inconsistent findings for diffusion capacity impairment after bleomycin vs. no bleomycin in CAYA cancer survivors. (4 studies, 1 significant effect, 3 non-significant effects; 384 participants)	
Comment:	Three studies with univariable analysis only, two reported results with p-values only and without confidence intervals. Outcome and cutoff value defined identical in three studies (DLCO< 75%predicted) and different in one study.	

5a Different doses

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Bleomycin exposure	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
5a What is the risk of <u>obstructive</u> abnormalities in CAYA survivors associated with different doses of bleomycin?	Record, 2016 (1)	143 CCS	Mean 14.1 ± 4.8 (SD)	13 low dose (<60IU/m²) 35 high dose (>= 60IU/m²)	Obstructive disease (FEV1, FEV1/FVC <80% predicted or FEF25–75% <68%) 11% (4/35) high 15% (2/13) low	Univariable comparison Chi2 low dose/high dose 0.72	1. No 2. Yes Wang X, Pediatr Pulmonol 2005; Hankinson JL, Am J Respir Crit Care Med 1999 3. No 4. Yes 5. No 6. Yes	Retrospective cohort SB: high risk AB: low risk DB: low risk CF: high risk
GRADE assessment:								
Study design:	+4	1 retrospective cohort study						
Study limitations:	-2	Severe limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding high in 1/1						
Consistency:	0	One study only						

Directness:	0	Population and outcomes broadly generalizable; PFT quality good (reference values and lung function procedures mentioned)
Precision:	-1	Precision cannot be judged as results are shown as p-value only, univariable analysis, only one study
Publication bias:	0	Publication bias unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No clear dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:	⊕⊖⊖⊖ VERY LOW	
Conclusion:	No significant effect for obstructive abnormalities in CAYA cancer survivors exposed to higher doses (≥60IU/m²) of bleomycin vs. lower doses (<60IU/m²). (1 study; 143 participants, 34 exposed to bleomycin)	
Comments:	Results reported from univariable analysis and as p-values only. Small sample size exposed to bleomycin in total.	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Bleomycin exposure	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
5a What is the risk of restrictive abnormalities in CAYA survivors associated with different doses of bleomycin?	Record, 2016 (1)	143 CCS	Mean 14.1 ± 4.8 (SD)	13 low dose (<60IU/m²) 35 high dose (>= 60IU/m²)	Restrictive disease (TLC<80% predicted) 17.1% (6/35) high 0% low	Univariable comparison Chi2 low dose/high dose 0.05	1. No 2. Yes Wang X, Pediatr Pulmonol 2005; Hankinson JL, Am J Respir Crit Care Med 1999 3. No 4. Yes 5. No 6. Yes	Retrospective cohort SB: high risk AB: low risk DB: low risk CF: high risk

GRADE assessment:		
Study design:	+4	1 retrospective cohort study
Study limitations:	-2	Severe limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding high in 1/1
Consistency:	0	One study only
Directness:	0	Population and outcomes broadly generalizable; PFT quality good (reference values and lung function procedures mentioned)
Precision:	-1	Precision cannot be judged as results are shown as p-value only, univariable analysis
Publication bias:	0	Publication bias unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No clear dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:	⊕⊖⊖⊖ VERY LOW	
Conclusion:	Increased risk for restrictive abnormalities (TLC) in CAYA cancer survivors after higher doses (≥60IU/m²) of bleomycin vs. lower doses (<60IU/m²) of bleomycin in CAYA cancer survivors. (1 study; 143 participants)	
Comments:	Results reported from univariable analysis and as p-values only. Small sample size exposed to bleomycin in total.	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Bleomycin exposure	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias

5a What is the risk of <u>hyperinflation</u> in CAYA survivors associated with different doses of bleomycin?	Record, 2016 (1)	143 CCS	Mean 14.1 ± 4.8 (SD)	13 low dose (<60IU/m²) 35 high dose (≤60IU/m²)	Hyperinflation (RV >120%predicted or RV/TLC >28% predicted) 25.7% (9/35) high 7.7% (1/13) low	Univariable comparison Chi2 low dose/high dose 0.14	1. No 2. Yes Wang X, Pediatr Pulmonol 2005; Hankinson JL, Am J Respir Crit Care Med 1999 3. No 4. Yes 5. No 6. Yes	Retrospective cohort SB: high risk AB: low risk DB: low risk CF: high risk

GRADE assessment:		
<u>Study design:</u>	+4	1 retrospective cohort study
<u>Study limitations:</u>	-2	Severe limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding high in 1/1
<u>Consistency:</u>	0	One study only
<u>Directness:</u>	0	Population and outcomes broadly generalizable; PFT quality good (reference values and lung function procedures mentioned)
<u>Precision:</u>	-1	Precision cannot be judged as results are shown as p-value only, univariable analysis
<u>Publication bias:</u>	0	Publication bias unlikely
<u>Effect size:</u>	0	No large magnitude of effect
<u>Dose-response:</u>	0	No clear dose response relationship
<u>Plausible confounding:</u>	0	No plausible confounding
Quality of evidence:	⊕⊖⊖⊖ VERY LOW	
Conclusion:	No significant effect on hyperinflation (RV, RV/TLC) in CAYA cancer survivors after higher doses (≥60IU/m²) of bleomycin vs. lower doses (<60IU/m²) of bleomycin. (1 study; 143 participants, 34 exposed to bleomycin)	
Comments:	Results reported as univariable analysis and p-values only. Small sample size exposed to bleomycin in total.	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Bleomycin exposure	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
5a What is the risk of <u>diffusion capacity impairment</u> in CAYA survivors associated with different doses of bleomycin?	Marina 1995 (15)	37 Hodgkin Lymphoma CCS	Median 7.7 (range 4.7-10.5)	37 (100%)	Cumulative dose of bleomycin and change in DLCO% predicted (DLCO <80% pred) Cumulative dose of bleomycin and change in DLCO/VA% predicted (DLCO <80% pred)	Cumulative dose of bleomycin (cont.) p=0.98 p=0.92	1. No 2. Yes Polgar G, 1971; Hsu KH, J Pediatr 1979; Goldman HI, Am Rev Tuberc, 1959; Morris JF, Am Rev Respir Dis, 1971; Weng TR, Am Rev Respir Dis, 1969; Miller A, Am Rev Respir Dis, 1983 3. No 4. Yes 5. No 6. No	Prospective cohort SB: Low risk AB: Low risk DB: Unclear CF: High risk
	Zorzi 2015 (16)	143 CCS	Median 4.4 (2 – 7.4)	86 (60%)		Cumulative dose of bleomycin (cont.) (1U/m2 increase of bleomycin)	1. No 2. Yes Stanojevic S, Am J Respir Crit Care Med, 2008; Wanger J, Eur	Retrospective cross-sectional SB: high risk AB: low risk

					Total 19% (27/143) with abnormal DLCO (DLCO <80% pred)	OR (95%CI) No association with abnormal DLCO (p=0.07)	Respir J, 2005; Weng TR, Am Rev Respir Dis, 1969; Pellegrino R, Eur Respir J, 2005; reference equations from Sick Children 3. No 4. No 5. No 6. No	DB: low risk CF: Unclear
	Mittal 2021 (17)	119 Hodgkin lymphoma CCS with DLCO	Median 10.3yr (6.04-16.8)	100%	DLCO in CCS exposed to <80mg/m2 vs. >80mg/m2 bleomycin	OR (95%CI) OR 2.12 (95%CI 0.99 – 4.49), p=0.051	1. Yes 2. Yes Quanjer, Pellegrino 3. No 4. Yes (ERS/ATS) 5. No 6. No	Prospective cohort SB: high risk AB: low risk DB: unclear CF: high risk

GRADE assessment:		
Study design:	+4	2 prospective cohort studies, 1 retrospective cross-sectional study
Study limitations:	-2	Severe limitations: Selection bias high in 2/3, low in 1/2; Attrition bias low in 3/3; Detection bias low in 1/3, unclear in 2/3; Confounding high in 2/3, unclear in 1/2
Consistency:	0	No inconsistency. All studies show no significant association between cumulative dose of bleomycin and diffusion capacity impairment.
Directness:	-1	Population and outcomes broadly generalizable; PFT quality unsure (all studies mention reference values, one mentions lung function procedures used)
Precision:	-1	Important imprecision, 2/3 show show p-value only, 1/3 report Odds Ratio and 95%CI, allreport univariable analysis only
Publication bias:	0	Publication bias unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No clear dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:	⊕⊖⊖⊖ VERY LOW	
Conclusion:	No significant effect on diffusion capacity impairment after higher doses of bleomycin vs. lower doses of bleomycin in CAYA cancer survivors. (3 studies; 3 non-significant effects; 299 participants, 242 participants exposed to bleomycin)	
Comments:	All studies report their results as univariable analysis only. Homogeneous outcome and cutoff definition across all studies.	

5b Age at exposure

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Bleomycin exposure	Pulmonary function Outcomes	Effect size	Risk of bias
5b What is the risk in younger compared to older age at treatment?							

No study

PICO 6: Busulfan

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Busulfan exposure	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias

6 What is the risk of <u>obstructive</u> abnormalities in CAYA treated with busulfan compared to CAYA not treated with busulfan?

No study

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Busulfan exposure	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
6 What is the risk of <u>restrictive</u> abnormalities in CAYA treated with busulfan compared to CAYA not treated with busulfan?	Armenian, 2015 (14)	121 CCS	Median 17.1 (6.3-40.1)	15 (12.4%)	29 Restrictive (TLC<75% and FEV1≥80% predicted) 13% (3/15) busulfan 24% (26/106) no busulfan	Univariable logistic regression Odds Ratio (95%CI) 0.8 (0.2-2.9)	1. Yes 2. No 3. No 4. Yes: ATS, Miller MR, Eur Respir J, 2005 5. No 6. Yes	Prospective cohort SB: Low risk AB: low risk DB: low risk CF: high risk

GRADE assessment:		
<u>Study design:</u>	+4	Prospective cohort study
<u>Study limitations:</u>	-1	Some limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding high in 1/1
<u>Consistency:</u>	0	One study only
<u>Directness:</u>	-1	Population and outcomes broadly generalizable; PFT quality unsure (no references mentioned, lung function procedure mentioned)
<u>Precision:</u>	-1	One study only, univariable comparison, results shown as OR and 95%CI
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	0	No large magnitude of effect
<u>Dose-response:</u>	0	Not applicable
<u>Plausible confounding:</u>	0	No plausible confounding

Quality of evidence:	⨁⊖⊖⊖ VERY LOW
Conclusion:	No significant effect on restrictive abnormalities (TLC<75% and FEV1≥80% predicted) after busulfan vs. no busulfan in CAYA cancer survivors. (1 study; 121 participants; 15 participants exposed to busulfan)
Conclusion:	Only univariable comparison between CCS exposed to busulfan and not; small sample size exposed to busulfan (12%)

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Busulfan exposure	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
6 What is the risk of <u>hyperinflation</u> in CAYA treated with busulfan compared to CAYA not treated with busulfan?								

No study

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Busulfan exposure	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
6 What is the risk of diffusion capacity impairment in CAYA treated with busulfan compared to CAYA not treated with busulfan?	Armenian, 2015 (13)	121 CCS	Median 17.1 (6.3-40.1)	15 (12.4%)	42 Diffusion impairment (DLCOcorr<75% predicted) 13% (3/15) busulfan 37% (39/106) no busulfan	Univariable logistic regression Odds Ratio (95%CI) 0.4 (0.1-1.6)	1. Yes 2. No 3. No 4. Yes: ATS, Miller MR, Eur Respir J, 2005 5. No 6. Yes	Prospective cohort SB: Low risk AB: low risk DB: low risk CF: high risk

GRADE assessment:		
Study design:	+4	Prospective cohort study
Study limitations:	-1	Some limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding high in 1/1
Consistency:	0	One study only
Directness:	-1	Population and outcome broadly generalizable; PFT quality unsure (no references mentioned, lung function procedure mentioned)
Precision:	-1	One study only, univariable comparison, results shown as OR and 95%CI
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:	⊕⊖⊖⊖ VERY LOW	
Conclusion:	No significant effect on diffusion capacity impairment (DLCO) after busulfan vs. no busulfan in CAYA cancer survivors. (1 study; 121 participants; 15 participants exposed to busulfan)	
Conclusion:	Only univariable comparison between CCS exposed to busulfan and not exposed	

6a Different doses

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Busulfan exposure	Pulmonary function Outcomes	Effect size	Risk of bias
6a What is the risk associated with different doses?							

No study

6b Age at exposure

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Busulfan exposure	Pulmonary function Outcomes	Effect size	Risk of bias
6b What is the risk in younger compared to older age at treatment? → No study							

No study

PICO 7: Nitrosureas

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Nitrosurea exposure	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
7 What is the risk of <u>obstructive</u> abnormalities in CAYA treated with nitrosureas compared to CAYA not treated with nitrosureas?								

No study

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Nitrosurea exposure	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
7 What is the risk of <u>restrictive</u> abnormalities in CAYA treated with nitrosureas compared to CAYA not treated with nitrosureas?	Armenian, 2015 (13)	121 CAYA	Median 17.1 yrs (6.3-40.1 yrs)	9.9%	Total 29 restrictive (TLC<75% and FEV1≥80% predicted) 25% (3/12) nitrosurea 24% (26/109) no nitrosurea	Univariable logistic regression Odds Ratio (95%CI) 1.1 (0.3-4.2)	1. Yes 2. No 3. No 4. Yes: ATS 5. No 6. Yes	Prospective cohort SB: Low risk AB: low risk DB: low risk CF: high risk

GRADE assessment:		
<u>Study design:</u>	+4	1 prospective cohort study
<u>Study limitations:</u>	-1	Some limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding high in 1/1
<u>Consistency:</u>	0	One study only
<u>Directness:</u>	-1	Population and outcomes broadly generalizable, PFT quality unsure (no reference mentioned, lung function procedure mentioned)
<u>Precision:</u>	-1	One study only, univariable analysis, results shown as OR with 95%CI
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	0	No large magnitude of effect
<u>Dose-response:</u>	0	Not applicable
<u>Plausible confounding:</u>	0	No plausible confounding
Quality of evidence:	⊕⊖⊖⊖ Very low	
Conclusion:	No significant effect on restrictive abnormalities (TLC and FEV1) after nitrosureas vs. no nitrosureas in CAYA cancer survivors. (1 study; 121 participants; 12 exposed to nitrosureas)	
Comment:	Only one univariable comparison, small sample size exposed to nitrosureas	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Nitrosurea exposure	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
7 What is the risk of <u>hyperinflation</u> in CAYA treated with nitrosureas compared to CAYA not treated with nitrosureas?								

No study

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Nitrosurea exposure	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
7 What is the risk of <u>diffusion capacity impairment</u> in CAYA treated with nitrosureas compared to CAYA not treated with nitrosureas?	Armenian, 2015 (13)	121 CAYA	Median 17.1 yrs (6.3-40.1 yrs)	9.9%	Total 42 diffusion abnormality (DLCO<75% predicted) 42% (5/12) nitrosureas 34% (37/109) no nitrosureas	Univariable logistic regression Odds Ratio (95%CI) 0.4 (0.6-4.7)	1. Yes 2. No 3. No 4. Yes: ATS 5. No 6. Yes	Prospective cohort SB: Low risk AB: low risk DB: low risk CF: high risk

GRADE assessment:		
<u>Study design:</u>	+4	1 prospective cohort study
<u>Study limitations:</u>	-1	Some limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding high in 1/1
<u>Consistency:</u>	0	One study only
<u>Directness:</u>	-1	Population and outcomes broadly generalizable, PFT quality unsure (no reference mentioned, lung function procedure mentioned)
<u>Precision:</u>	-1	One study only, univariable analysis, results shown as OR with 95%CI
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	0	No large magnitude of effect
<u>Dose-response:</u>	0	Not applicable
<u>Plausible confounding:</u>	0	No plausible confounding
Quality of evidence:	⊕⊖⊖⊖ Very low	
Conclusion:	No significant effect on diffusion capacity impairment (DLCO) after nitrosureas vs. no nitrosureas in CAYA cancer survivors. (1 study; 121 participants; 12 exposed to nitrosureas)	
Comment:	Only one univariable comparison, small sample size exposed to nitrosureas	

7a Different doses

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Nitrosurea exposure	Pulmonary function Outcomes	Effect size	Risk of bias
7a What is the risk associated with different doses?							

No study

7b Age at exposure

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Nitrosurea exposure	Pulmonary function Outcomes	Effect size	Risk of bias

7b What is the risk in younger compared to older age at treatment?

No study

PICO 8: Radiotherapy

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Radiotherapy exposing lung tissue	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
8 What is the risk of <u>obstructive</u> abnormalities in CAYA treated with radiotherapy exposing lung tissue compared to CAYA not treated with radiotherapy exposing lung tissue?	Oguz 2007 (18)	75 Lymphoma survivors	Median 5 (2-13)	Group 1: Chemo and Radio (n=23) Group 2: Chemo only (n=52)	Mean (±SD) of selected % predicted values **FEV1** Group 1: 95.43 (± 16.47) Group 2: 105.09 (± 19.01) **FEV1/FVC** Group 1: 96.43 (± 9.15) Group 2: 99.88 (± 11.93)	Comparison Group I vs Group II (student t-test) p=0.038 p=0.221	1. No 2. Yes: References recommended by European Coal and Steel Community; Severity acc. to ATS pulmonary function laboratory guidelines 3. No 4. No 5. No 6. No	Retrospective cross-sectional SB unclear AB: low risk DB: unclear CF: unclear
	Jenney 1995 (8)	70 Leukemia survivors	Median 4.2 (0.6-18.5)	14% (CSI, n=10) 20% (TBI, n=14)	Number of CCS with respective parameter below predicted values 36/69 FEV1 <85% predicted 23/69 FEV1 <80% predicted	Multivariable analysis, CSI (yes/no) leads to reduction in FEV1: p<0.001	1. Yes 2. No 3. No 4. No 5. No 6. No	Prospective cross-sectional SB: high risk AB: low risk DB: unclear CF: unclear
	Record 2016 (1)	143 CCS	Mean 14.1 ±4.8	67.8% (n=97)	Obstructive (FVC, FEV1, FEV1/FVC <80% predicted or FEF25–75% <68%) 25% (24/97)radiotherapy 28% (13/46) no radiotherapy	Univariable comparison Chi2 radiation yes/no p=0.66	1. No 2. Yes: Wang X, Pediatr Pulmonol 2005; Hankinson JL, Am J Respir Crit Care Med 1999 3. No 4. Yes 5. No 6. Yes	Retrospective cohort SB: high risk AB: low risk DB: low risk CF: high risk
	Stone 2020 (19)	62 high-risk neuroblastoma	Median 5.29 (0.24-15.24)	34% (n=21)	Comparison of CCS treated with radiotherapy versus no radiotherapy **FEV1** (FEV1 <80% pred) RT yes: 71.4% abnormal RT no: 34.2% abnormal	OR, 95%CI 4.29 (1.35 – 13.58), p=0.005	1. No 2. Yes 3. No 4. Yes (ATS) 5. No 6. No	Prospective cohort SB: high risk AB: low risk DB: low risk CF: high risk
	Otth 2021 (20)	72 CCS exposed to HSCT	Median 9.4 (6.1 – 12.3)	70% (n=52)		mixed effects multivariable linear regression analysis	1. Yes 2. Yes 3. No 4. No	Retrospective cohort SB: high risk AB: low risk DB: low risk

				FEV1 Effect of radiotherapy vs. no radiotherapy on longitudinal changes in FEV1 (intercept) **MMEF** Effect of radiotherapy vs. no radiotherapy on longitudinal changes in MMEF (intercept)	Coefficient -1.306 95%CI -2.055 - -0.558 p=0.001 Coefficient -0.664 95%CI -1.583 – 0.253 p=0.156	5. Yes 6. No	CF: low risk

GRADE assessment:		
Study design:	+4	2 retrospective cohort study, 1 retrospective cross-sectional study, 1 prospective cross-sectional study, 1 prospective cohort study
Study limitations:	-2	Some limitations: Selection bias high in 4/5, unclear in 1/3; Attrition bias low in 4/5; Detection bias low in 3/5, unclear in 2/3; Confounding high in 2/5, low in 1/5, unclear in 2/5
Consistency:	-1	Some inconsistency. Four studies show significant effect of radiotherapy exposing lung tissue on FEV1, one study on MMEF, no significant association for FEV1/FVC and a non-significant inverse effect on "obstructive", where non-exposed CAYA cancer survivors show more often obstructive abnormalities than exposed
Directness:	-1	Population and outcomes broadly generalizable, PFT quality unsure (reference mentioned in 5/5, lung function procedure mentioned in 0/5)
Precision:	-1	Important imprecision, 3/5 report p-values only, 2/5 report 95%CI, 1/5 performed univariable regression analysis, 2/5 performed multivariable analysis
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:	⊕⊖⊖⊖ Very low	
Conclusion:	Increased risk for obstructive abnormalities (FEV1, MMEF) after radiotherapy exposing the lung tissue vs. no radiotherapy in CAYA cancer survivors. (5 studies; 3 studies significant effect [FEV1] and 1 study on MMEF, 1 study non-significant effect ["obstructive]; 422 participants; 217 exposed to radiotherapy exposing lung tissue)	
Comment:	Outcome assessed differently (FEV1, MMEF, "obstructive") and cutoff values differ between studies.	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Radiotherapy exposing lung tissue	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
8 What is the risk of restrictive abnormalities in CAYA treated with radiotherapy exposing lung tissue compared to CAYA not treated with radiotherapy	Oguz 2007 (17)	75 Lymphoma survivors	Median 5 (2-13)	Group 1: Chemo and Radio (n=23) Group 2: Chemo only (n=52)	Mean (±SD) of selected % predicted values **FVC** Group 1: 101.17 (± 19.93) Group 2: 102.94 (± 18.11) **TLC** Group 1: 102.74 (± 15.63) Group 2: 106.73 (± 17.46)	Comparison Group I vs Group II (student t-test) p=0.706 p=0.349	1. No 2. Yes: references recommended by European Coal and Steel Community; Severity acc. to ATS pulmonary function laboratory guidelines 3. No 4. No 5. No 6. No	Retrospective cross-sectional SB unclear AB: low risk DB: unclear CF: unclear

exposing lung tissue?	Jenney 1995 (8)	70 Leukemia survivors	Median 4.2 (0.6-18.5)	14% (CSI, n=10) 20% (TBI, n=14)	Number of CCS with respective parameter below predicted values 32/69 FVC <85% predicted 26/69 TLC <85% predicted 20/69 FVC <80% predicted 20/69 TLC <80% predicted	Multivariable analysis, CSI leads to reduction in FVC and TLC: p<0.001	1. Yes 2. No 3. No 4. No 5. No 6. No	Prospective cross-sectional SB: high risk AB: low risk DB: unclear CF: unclear
	Record 2016 (1)	143 CCS	Mean 14.1 ±4.8 yrs	67.8% (n=97)	Restrictive (TLC<80% predicted) 11% (11/97) radiotherapy 17% (8/46) no radiotherapy	Univariable comparison Chi2 radiation yes/no p=0.33	1. No 2. Yes Wang X, Pediatr Pulmonol 2005; Hankinson JL, Am J Respir Crit Care Med 1999 3. No 4. Yes 5. No 6. Yes	Retrospective cohort SB: high risk AB: low risk DB: low risk CF: high risk
	Mulder 2011 (9)	193 CCS	Median 17.9 (5.6-36.8)	40.9% (n=79)	Total 28 restrictive (TLC OR FVC <75%) Of those Exposed: 35%	Odds Ratio (95%CI) for radiotherapy yes/no 12.87 (3.37-49.08)	1. No 2. No 3. No 4. No 5. No 6. No	Retrospective cohort SB: low risk AB: low risk DB: unclear CF: low risk
	Stone 2020 (19)	62 high-risk neuroblastoma	Median 5.29 (0.24-15.24)	34% (n=21)	**FVC** (FVC <80% pred) RT yes: 76.2% abnormal RT no: 41.7% abnormal **TLC** (TLC <80% pred) RT yes: 66.7% abnormal RT no: 35.4% abnormal	OR, 95%CI 4.40 (1.34 – 14.51) p=0.010 4.33 (1.39 – 13.50), p=0.005	1. No 2. Yes 3. No 4. Yes (ATS) 5. No 6. No	Prospective cohort SB: high risk AB: low risk DB: low risk CF: high risk
	Otth 2021 (20)	72 CCS exposed to HSCT	Median 9.4 (6.1 – 12.3)	70% (n=52)	**FVC** Effect of radiotherapy vs. no radiotherapy on longitudinal changes in FVC **TLC**	mixed effects multivariable linear regression analysis Coefficient -1.473 95%CI -2.207 – -0.739 p=<0.001	1. Yes 2. Yes 3. No 4. No 5. Yes 6. No	Retrospective cohort SB: high risk AB: low risk DB: low risk CF: low risk

			Effect of radiotherapy vs. no radiotherapy on longitudinal changes in TLC	Coefficient -0.717 95%CI -2.051 – 0.616; p=0.292

GRADE assessment:		
Study design:	+4	3 retrospective cohort studies, 1 retrospective cross-sectional study, 1 prospective cross-sectional study, 1 prospective cohort study
Study limitations:	-2	Some limitations: Selection bias high in 4/6, low in 1/6, unclear in 1/6; Attrition bias low in 6/6; Detection bias low in 3/6, unclear in 3/6; Confounding high in 3/6, low in 1/6, unclear in 2/6
Consistency:	0	Some inconsistency. Four studies show significant effect of radiotherapy exposing lung tissue on restrictive parameter (FVC, TLC, "restrictive"), one has only small sample of exposed CAYA survivors and the second has a large confidence interval. No significant association in the other two studies.
Directness:	-1	Population and outcomes broadly generalizable, PFT quality unsure (reference mentioned in 4/6, lung function procedure mentioned in 2/6)
Precision:	-1	Important imprecision, precision cannot be judged as 3/6 report p-values only, 3/6 shows OR and 95%CI but some with large confidence interval, 2/6 performed multivariable analysis, 1/6 performed univariable regression analysis
Publication bias:	0	Unlikely
Effect size:	1	Large magnitude of effect in one study
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:	⊕⊖⊖⊖ Very low	
Conclusion:	Increased risk for restrictive abnormalities (FVC or TLC) after radiotherapy exposing lung tissue vs. no radiotherapy in CAYA cancer survivors. (6 studies; 4 studies significant effect, 2 studies non-significant effect; 617 participants; 296 exposed to radiotherapy exposing lung tissue)	
Comment:	3/6 studies show p-value only. Outcome and cutoff values differ between the studies.	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Radiotherapy exposing lung tissue	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
8 What is the risk of hyperinflation in CAYA treated with radiotherapy exposing lung tissue compared to CAYA not treated with radiotherapy exposing lung tissue?	Oguz 2007 (17)	75 Lymphoma survivors	Median 5 (2-13)	Group 1: Chemo and Radio (n=23) Group 2: Chemo only (n=52)	Mean (±SD) of selected % predicted values **RV** Group 1: 113.35 (± 28.53) Group 2: 126.71 (± 24.63) **RV/TLC** Group 1: 25.39 (± 5.31) Group 2: 27.71 (± 4.92)	Comparison Group I vs Group II (student t-test) p=0.043 p=0.062	1. No 2. Yes: references recommended by European Coal and Steel Community; Severity acc. to ATS pulmonary function laboratory guidelines 3. No 4. No 5. No 6. No	Retrospective cross-sectional SB unclear AB: low risk DB: unclear CF: unclear
	Record 2016 (1)	143 CCS	Mean 14.1 ±4.8	67.8% (n=97)	hyperinflation (RV >120%pred or RV/TLC >28% pred) 46% (45/97) radiotherapy 30% (14/46) no radiotherapy	Univariable comparison Chi2 radiation yes/no p=0.07	1. No 2. Yes: Wang X, Pediatr Pulmonol 2005; Hankinson JL, Am J Respir Crit Care Med 1999 3. No 4. Yes 5. No 6. Yes	Retrospective cohort SB: high risk AB: low risk DB: low risk CF: high risk

	Otth 2021 (20)	72 CCS exposed to HSCT	Median 9.4 (6.1 – 12.3)	70% (n=52)	**RV** Effect of radiotherapy vs. no radiotherapy on longitudinal changes in TLC	mixed effects multivariable linear regression analysis Coefficient 0.663 95%CI -0.307 – 1.634; p=0.181	1. Yes 2. Yes 3. No 4. No 5. Yes 6. No	Retrospective cohort SB: high risk AB: low risk DB: low risk CF: low risk

GRADE assessment:		
Study design:	+4	1 retrospective cohort studies, 1 retrospective cross-sectional study, 1 retrospective cohort study
Study limitations:	-2	Some limitations: Selection bias high in 2/3, unclear in 1/3; Attrition bias low in 3/3; Detection bias low in 2/3, unclear in 1/3; Confounding high in 1/3, low in 1/3, unclear in 1/3
Consistency:	0	Some inconsistency between studies. Two studies show an association between hyperinflation and radiotherapy exposing the lung tissue. One study shows no association between exposure and longitudinal changes.
Directness:	-1	Population and outcomes broadly generalizable, PFT quality unsure (reference mentioned in 3/3, lung function procedure mentioned in 1/3)
Precision:	-1	Important imprecision, precision cannot be judged as 2/2 report p-values only and 2/2 performed unviable analysis only
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:	⊕⊖⊖⊖ Very low	
Conclusion:	Increased risk for hyperinflation (RV, RV/TLC) after radiotherapy exposing the lung tissue vs. no radiotherapy in CAYA cancer survivors in 2 studies and a trend in one study (3 studies; 292participants; 172participants with radiotherapy exposing the lung tissue)	
Comment:	2/3 studies reported p-values only with a trend is towards more hyperinflation in exposed CAYA cancer survivors. Outcome definition differs between the studies.	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Radiotherapy exposing lung tissue	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
8 What is the risk of diffusion capacity impairment in CAYA treated with radiotherapy exposing lung tissue compared to CAYA not treated with radiotherapy exposing lung tissue?	Oguz 2007 (17)	75 Lymphoma survivors	Median 5 (2-13)	Group 1: Chemo and Radio (n=23) Group 2: Chemo only (n=52)	Mean (±SD) of selected % predicted values DLCO Group 1: 101.35 (± 22.17) Group 2: 112.65 (± 4.92)	Comparison Group I vs Group II (student t-test) p=0.025	1. No 2. Yes: references recommended by European Coal and Steel Community; Severity acc. to ATS pulmonary function laboratory guidelines 3. No 4. No 5. No 6. No	Retrospective cross-sectional SB unclear AB: low risk DB: unclear CF: unclear
	Jenney 1995 (8)	70 Leukemia survivors	Median 4.2 (0.6-18.5)	14% (CSI, n=10) 20% (TBI, n=14)	Number of CCS with respective parameter below predicted values	Multivariable analysis, CSI leads to reduction in DLCO: p<0.030	1. Yes 2. No 3. No 4. No	Prospective cross-sectional SB: high risk AB: low risk

					29/69 DLCO <85% predicted 19/69 DLCO <80% predicted		5. No 6. No	DB: unclear CF: unclear
	Zorzi 2015 (16)	143 CCS (Hodgkin, extracranial germ cell tumor)	Median 4.4 (2 – 7.4)	60% (n=86)	19% (27/143) with abnormal DLCO (DLCO <80%)	No association (p=0.83)	1. No 2. Yes Stanojevic S, Am J Respir Crit Care Med, 2008; Wanger J, Eur Respir J, 2005; Weng TR, Am Rev Respir Dis, 1969; Pellegrino R, Eur Respir J, 2005; reference equations from Sick Children 3. No 4. No 5. No 6. No	Retrospective cross-sectional SB: high risk AB: low risk DB: low risk CF: unclear
	Mulder 2011 (9)	193 CCS	Median 17.9 (5.6-36.8)	40.9% (n=79)	75/188 Diffusion impairment (DLCO <75%)	Odds Ratio (95%CI) for radiotherapy yes/no 5.84 (1.88-18.14)	1. No 2. No 3. No 4. No 5. No 6. No	Retrospective cohort SB: low risk AB: low risk DB: unclear CF: low risk
	Stone 2020 (19)	62 high-risk neuroblastoma	Median 5.29 (0.24-15.24)	34% (n=21)	**DLCO** (DLCO <80% pred) RT yes: 2.4% abnormal RT no: 66.7% abnormal	OR, 95%CI 2.05 (0.49 – 8.62), p=0.339	1. No 2. Yes 3. No 4. Yes (ATS) 5. No 6. No	Prospective cohort SB: high risk AB: low risk DB: low risk CF: high risk
	Otth 2021 (20)	72 CCS exposed to HSCT	Median 9.4 (6.1 – 12.3)	70% (n=52)	**DLCO** Effect of radiotherapy vs. no radiotherapy on longitudinal changes in DLCO	mixed effects multivariable linear regression analysis Coefficient -1.279 95%CI -2.773 - 0.213; p=0.093	1. Yes 2. Yes 3. No 4. No 5. Yes 6. No	Retrospective cohort SB: high risk AB: low risk DB: low risk CF: low risk

GRADE assessment:

Study design:	+4	2 retrospective cohort study, 2 retrospective cross-sectional studies, 1 prospective cross-sectional study, 1 prospective cohort study
Study limitations:	-2	Some limitations: Selection bias high in 4/6, low in 1/4, unclear in 1/4; Attrition bias low in 6/6; Detection bias low in 3/6, unclear in 3/6; Confounding low in 2/6, unclear in 4/6
Consistency:	0	No important inconsistency. Most studies show diffusion capacity impairment in CAYA cancer survivors exposed to radiotherapy exposing lung tissue compared to CAYA cancer survivors not exposed.
Directness:	-1	Population and outcomes broadly generalizable, PFT quality unsure (reference mentioned in 4/6, lung function procedure mentioned in 1/6)

Precision:	-1	Important imprecision, in 3/6 as results are shown with p-value only, 1/6 has large confidence interval, 2/6 perforemd multivariable analysis, 1/5 performed univariable regression analysis
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:	⊕⊖⊖⊖ Very low	
Conclusion:	Increased risk for diffusion capacity impairment (DLCO) after radiotherapy exposing the lung tissue vs. no radiotherapy in CAYA cancer survivors. (6 studies; 3 studies significant effect, 3 study non-significant effect; 617participants; 296 participants with radiotherapy exposing the lung tissue)	
Comment:	Three studies show p-value only. Outcome definition and cutoff values differ between the studies.	

8a Different doses

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Radiotherapy exposing lung tissue	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
8a What is the risk for <u>obstructive</u> abnormalities associated with different doses and volumes of radiotherapy? - **dose-volume relationship** **- impact of dose per fraction**	Weiner 2006 (21)	30 CSS (Wilms tumor, Hodgkin disease, Sarcoma, Hepato-blastoma)	Median 2.79 (range 0-13.7)	100% (n=30)	- FEV1 z-score - FEV1 z-score	No correlation between severity of abnormal FEV1 z-score and total radiation dose: - r^2=0.002 (very weak) No correlation between severity of abnormal FEV1 z-score and total radiation dose after taking body length into account: - r^2=0.002 (very weak)	1. No 2. Yes: Wang X, Pediatr Pulmonol, 1993; Rosenthal M, Thorax 1993 3. No 4. Yes 5. No 6. No	Retrospective cohort SB: High Risk AB: High risk DB: Low risk CF: High Risk
	Green 2016 (22)	606 CCS (FEV1, FVC) 597 CCS (TLC, DLCO)	Median 21.9	76.7% (n=465)	Proportion of CCS with pulmonary function parameter below %pred or LLN for whole cohort 51% FEV1 <80% pred 49% FEV1 <LLN	Multivariable log-binomial regression: Outcome: V10 (per 10% increase) Relative Risk (95%CI, p-value) 1.07 (1.04–1.09, <0.001) 1.06 (1.04-1.09, <0.001)	1. No 2. Yes Wanger J, Eur Respir J, 2005; Goldman HI, Am Rev Tuberc, 1959; Boren HG, Am J Med, 1966; Miller A, Am Rev Respir Dis, 1983; Quanjer PH, lookup table, accessed 2015; Quanjer PH, Eur Respir J, 2012 3. Yes 4. Yes: ATS 5. No 6. No	Prospective cohort SB: High risk AB: Low risk DB: Unclear CF: Low risk

	De 2015 (12)	49 Osteo sarcoma	Median 2.91 (range 0.01-8.28)	100% (n=49)	Proportion of CCS with abnormal results per lung function parameter FEV1 <80% pred: 29% (14/49) FEF25–75% <68% pred: 20% (10/49) Obstructive disease (FEV1/FVC <80%, FEV1<80% or FEF25-75<68% with normal TLC): 24% (12/49)	Logistic regression with radiation dose in Gy (cont.) and normal/ abnormal parameter Odds Ratio (p-value) Mean dose: 1.20; 0.01 Max dose: 1.12; <0.01 Mean dose: 1.18; <0.01 Max dose: 1.06; <0.05 Mean dose: 0.99; NS Max dose: 1.03; NS Prescribed dose: 1.05; NS	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Wang X, Pediatr Pulmonol, 1993 3. No 4. Yes: ATS 5. No 6. No	Retrospective cohort SB: High Risk AB: High Risk DB: Low risk CF: High Risk

GRADE assessment:		
Study design:	+4	2 retrospective cohort studies, 1 prospective cohort study
Study limitations:	-3	Some limitations: Selection bias high in 3/3; Attrition bias high in 2/3, low in 1/3; Detection bias low in 2/3, unclear in 1/2; Confounding high in 2/3
Consistency:	0	Most studies show slightly increased risk for indicators of obstructive abnormalities below predicted or LLN with higher doses of radiotherapy.
Directness:	-1	Results are direct, population and outcomes broadly generalizable, PFT quality good (in 3/3 reference values and guidelines mentioned)
Precision:	-1	Important imprecision 1/3 show precise results with small confidence interval; 1/3 shows correlation coefficient only; 1/3 shows effect size but without 95%CI
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	+1	Dose-response relationship
Plausible confounding:	0	No evidence of possible confounding
Quality of evidence:	⊕⊖⊖⊖ Very low	
Conclusion:	Increased risk for obstructive abnormalities (FEV1, FEF25.75%) after increasing doses radiotherapy exposing lung tissue in CAYA cancer survivors (3 studies; 2 significant effects [FEV1, FEF25.75%], 1 non-significant effect [obstructive, FEV1]; 685 participants; 544 participants exposed to radiotherapy)	
Comments:	One study shows correlation coefficient only	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Radiotherapy exposing lung tissue	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
8a What is the risk for restrictive abnormalities associated with different doses and volumes of radiotherapy? - **dose-volume relationship**	Weiner 2006 (18)	30 CSS (Wilms tumor, Hodgkin disease, Sarcoma, Hepato-blastoma)	Median 2.79 (range 0-13.7)	100% (n=30)	-TLC z-score (n=23)	No correlation between severity of abnormal FEV1, TCL, and DLCO (z-score) and total radiation dose: - r^2=0.06 (very weak) No correlation between severity of abnormal TCL (z-score) and total radiation dose after	1. No 2. Yes: Wang X, Pediatr Pulmonol, 1993; Rosenthal M, Thorax 1993 3. No 4. Yes 5. No 6. No	Retrospective cohort SB: High Risk AB: High risk DB: Low risk CF: High Risk

- impact of dose per fraction				- TLC z-score (n=23)	taking body length into account: - r^2=0.027 (very weak)		
	Green 2016 (19)	606 CCS (FEV1, FVC) 597 CCS (TLC, DLCO)	Median 21.9	76.7% (n=465)	Proportion of CCS with pulmonary function parameter below %pred or LLN in the whole cohort 47.2% FVC <80% pred 45.4% FVC < LLN 31.2% TLC <75% pred	Multivariable log-binomial regression: Outcome: V10 (per 10% increase) Relative Risk (95%CI, p-value) 1.08 (1.05–1.11, <0.001) 1.07 (1.04-1.10, <0.001) 1.07 (1.01–1.13, 0.019)	1. No 2. Yes Wanger J, Eur Respir J, 2005; Goldman HI, Am Rev Tuberc, 1959; Boren HG, Am J Med, 1966; Miller A, Am Rev Respir Dis, 1983; Quanjer PH, lookup table, accessed 2015; Quanjer PH, Eur Respir J, 2012 3. Yes 4. Yes: ATS 5. No 6. No	Prospective cohort SB: high risk AB: low risk DB: unclear CF: high risk
	Armenian, 2015 (14)	121 CAYA	Median 17.1 yrs (6.3-40.1)	73.6% (n=89) Categories: 26.4% No (Ref.) 49.6% ≤20Gy 24.0% >20Gy	Total 29 restrictive 13% (4/32) no radiation 45% (13/60) ≤20Gy, 41% (12/29) >20 Gy	Multivariable logistic regression Odds Ratio (95%CI) 1 ≤20Gy 1.6 (0.5-5.7) >20Gy 5.6 (1.5-2.1)	1. Yes 2. No 3. No 4. Yes: ATS 5. No 6. Yes	Prospective cohort SB: Low risk AB: low risk DB: low risk CF: high risk
	Green 2015 (10)	260 embryonal brain tumors	Minimum 2 yr	100% CSI (n=260)	Proportion of CCS with TLC below predicted after 60 months TLC < 75%: 11% *Unclear how many received proton and photon beam, but of initially 303 eligible patients only 20 had proton beam*	Larger **TLC% predicted**: photon beam CSI (p=0.002)	1. No 2. Yes: 10 different references for standardization 3. No 4. Yes: ATS 5. No 6. No	Prospective cohort SB: low risk AB: high risk DB: unclear CF: high risk
	De 2015 (12)	49 Osteo sarcoma	Median 2.91 (range 0.01-8.28)	100% (n=49)	Proportion of CCS with abnormal results per lung function parameter FVC <80% pred: 24% (12/49) TLC <77% pred: 15% (7/49)	Logistic regression analysis with radiation dose in Gy (cont.) and normal/ abnormal parameter Odds Ratio (p-value) Mean dose: 1.22; <0.01 Max dose: 1.10; <0.01 Mean dose: 1.30; <0.01 Max dose: 1.07; <0.05	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Wang X, Pediatr Pulmonol, 1993 3. No 4. Yes: ATS 5. No 6. No	Retrospective cohort SB: High Risk AB: High Risk DB: Low risk CF: High Risk

						The odds of developing restrictive abnormalities increased with increasing V dose beginning at V10		
					Restrictive (TLC <77%) 15% (7/49)	Mean dose: 1.30; <0.01 Max dose: 1.07; <0.05 Prescribed dose: 1.04; NS		

GRADE assessment:		
Study design:	+4	2 retrospective cohort studies 3 prospective cohort studies
Study limitations:	-3	Some limitations: Selection bias high in 3/5, low in 2/5; Attrition bias high in 3/5, low in 2/5; Detection bias low in 3/5, unclear in 2/5; Confounding high in 5/5,
Consistency:	0	Most studies show more restrictive abnormalities in CAYA cancer survivors exposed to increasing doses of radiotherapy to the thorax.
Directness:	-1	Results are direct, population and outcomes broadly generalizable, PFT quality unsure (in 1/5 no reference values stated and in 1/5 10 different references; in 1/5 no guidelines mentioned)
Precision:	-1	Important imprecision. 2/5 with multivariable analysis; 2/5 with effect size and small confidence intervals; in 2/5 precision cannot be judged as results are shown as coefficient or p-value only
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	+1	Dose-response relationship
Plausible confounding:	0	No evidence of possible confounding
Quality of evidence:		⊕⊖⊖⊖ Very low
Conclusion:		Increased risk for restrictive abnormalities after increasing doses of radiotherapy exposing lung tissue in CAYA cancer survivors. (5 studies; 1066 participants; 893 participants exposed to radiotherapy)
Comments:		Different cutoff values used between studies to define parameters as abnormal. One study shows correlation coefficient only

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Radiotherapy exposing lung tissue	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
8a What is the risk for <u>hyperinflation</u> associated with different doses and volumes of radiotherapy? **- dose-volume relationship** **- impact of dose per fraction**	De 2015 (12)	49 Osteo-sarcoma	Median 2.91 (range 0.01-8.28)	100% (n=49)	Proportion of CCS with abnormal results per lung function parameter RV/TLC: >123% pred: 20% (10/49) Hyperinflation	Logistic regression with radiation dose in Gy (cont.) and normal/ abnormal parameter Odds Ratio (p-value) Mean dose: 1.30; <0.01 Max dose: 1.26; <0.05 The odds of developing hyperinflation increased with increasing V dose beginning at V20 Mean dose: 1.29; <0.01 Max dose: 1.26; <0.01	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Wang X, Pediatr Pulmonol, 1993 3. No 4. Yes: ATS 5. No 6. No	Retrospective cohort SB: High Risk AB: High Risk DB: Low risk CF: High Risk

		(RV/TLC >28%): 20% (10/49)	Prescribed dose: 1.27; <0.01

GRADE assessment:		
Study design:	+4	1 retrospective cohort study
Study limitations:	-3	Important limitations: Selection bias high in 1/1; Attrition bias high in 1/1; Detection bias low in 1/1; Confounding high in 1/1
Consistency:	0	One study only
Directness:	0	Population and outcomes broadly generalizable, PFT quality good (reference values and guidelines used stated)
Precision:	-1	Important imprecision 1/1 sow results with OR but without 95%CI
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	+1	Dose response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ Very low
Conclusion:		Increased risk for hyperinflation after increasing doses of radiotherapy exposing lung tissue in CAYA cancer survivors (1 study; 49 participants; 49 participants exposed to radiation exposing the lung tissue)
Comment:		One study only with small sample size and effect size without confidence interval.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Radiotherapy exposing lung tissue	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
8a What is the risk for diffusion capacity impairment associated with different doses and volumes of radiotherapy? - **dose-volume relationship** **- impact of dose per fraction**	Weiner 2006 (18)	30 CSS (Wilms tumor, Hodgkin disease, Sarcoma, Hepato-blastoma)	Median 2.79 (range 0-13.7)	100% (n=30)	- DLCO z-score (n=21) - DLCO z-score (n=21)	No correlation between severity of abnormal FEV1, TCL, and DLCO (z-score) and total radiation dose: - r^2=0.13 (very weak) No correlation between severity of abnormal DLCO (z-score) and total radiation dose after taking body length into account: - r^2=0.03 (very weak)	1. No 2. Yes: Wang X, Pediatr Pulmonol, 1993; Rosenthal M, Thorax 1993 3. No 4. Yes 5. No 6. No	Retrospective cohort SB: High Risk AB: High risk DB: Low risk CF: High Risk

	Green 2016 (19)	606 CCS (FEV1, FVC) 597 CCS (TLC, DLCO)	Median 21.9	76.7% (n=465)	Proportion of CCS with pulmonary function parameter below %pred or LLN in the whole cohort 44.6% $DLCO_{corr}$ <75% pred	Multivariable log-binomial regression: Outcome: V10 (per 10% increase) Relative Risk (95%CI, p-value) 1.07 (1.04–1.10, <0.001)	1. No 2. Yes Wanger J, Eur Respir J, 2005; Goldman HI, Am Rev Tuberc, 1959; Boren HG, Am J Med, 1966; Miller A, Am Rev Respir Dis, 1983; Quanjer PH, lookup table, accessed 2015; Quanjer PH, Eur Respir J, 2012 3. Yes 4. Yes: ATS 5. No 6. No	Prospective cohort SB: high risk AB: low risk DB: unclear CF: high risk
	Armenian, 2015 (15)	121 CAYA	Median 17.1 (6.3-40.1)	73.6% (n=89) Categories: 26.4% No (Ref.) 49.6% ≤20Gy 24.0% >20Gy	Total 42 diffusion abnormality 9% (3/32) no radiation, 40% (24/60) ≤20Gy, 52% (15/29) >20Gy	Multivariable logistic regression Odds Ratio (95%CI) 1 6.4 (1.7-2.4) 11.3 (2.6-49.5)	1. Yes 2. No 3. No 4. Yes: ATS 5. No 6. Yes	Prospective cohort SB: Low risk AB: low risk DB: low risk CF: high risk
	Green 2015 (10)	260 embryonal brain tumors	Minimum 2 yr	100% CSI (n=260)	Proportion of CCS with DLCO below predicted 60 months after treatment - DLCO corr < 75% predicted 25% Unclear how many received proton and photon beam, but of initially 303 eligible patients only 20 had proton beam	Higher **DLCO% predicted** when treated with lower RT doses (≤2345 cGy) (p=0.032)	1. No 2. Yes: 10 different references for standardization 3. No 4. Yes: ATS 5. No 6. No	Prospective cohort SB: low risk AB: high risk DB: unclear CF: high risk
	De 2015 (12)	49 Osteo-sarcoma	Median 2.91 (range 0.01-8.28)	100% (n=49)	Proportion of CCS with abnormal results per lung function parameter $DLCO_{adj}$ <65% pred: 9% (4/49) DLCO <65%pred: 14% (6/49)	Logistic regression analysis with radiation dose in Gy (cont.) and normal/ abnormal parameter Odds Ratio (p-value) Mean dose: 1.27; <0.01 Max dose: 1.07; <0.05 Mean dose : 1.16; <0.05 Max dose: 1.05; NS Prescribed dose: 1.05; NS	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Wang X, Pediatr Pulmonol, 1993 3. No 4. Yes: ATS 5. No 6. No	Retrospective cohort SB: High Risk AB: High Risk DB: Low risk CF: High Risk
GRADE assessment: Study design:		+4	2 retrospective cohort studies 3 prospective cohort studies					

Study limitations:	-3	Important limitations: Selection bias high in 3/5, low in 2/5; Attrition bias high in 3/5, low in 2/5; Detection bias low in 3/5, unclear in 2/5; Confounding high in 5/5
Consistency:	0	No important inconsistency. Most studies show risk for more diffusion capacity impairment in CAYA cancer survivors treated with higher radiation doses. Only one study shows no correlation
Directness:	-1	Results are direct, population and outcomes broadly generalizable, PFT quality unsure (1/5 does not mention reference values used; 5/5 mention the use of guidelines)
Precision:	-1	Important imprecision; 2/5 performed multivariable analysis;21/5 shows effect size with small 95%CI; 1/5 shows effect size with large 95%CI; 1/5 shows effect size but without 95%CI, in 1/5 precision cannot be judged as result is shown with p-value only; 1/5 shows correlation coefficient only 2/6 have large confidence interval, 3/6 show no effect estimate but p-values 1/6 is a correlatin only
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	+1	Dose-repsonse relationship
Plausible confounding:	0	No evidence of possible confounding
Quality of evidence:	⊕⊖⊖⊖ Very low	
Conclusion:	Increased risk for diffusion capacity impairment after increasing doses of radiotherapy exposing the lung tissue in CAYA cancer survivors. (5 studies; 4 significant effects, 1 non-significant effect; 1057 participants; 893 participants exposed to radiotherapy)	
Comments:	Different cutoff values used between studies to define parameters as abnormal. One study shows correlation coefficient only	

8b Different radiotherapeutic fields

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Radiotherapy exposing lung tissue	Pulmonary function Outcomes	Effect size	Risk of bias
8b What is the risk in different radiotherapeutic fields? → No study							

8c Age at exposure

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Radiotherapy exposing lung tissue	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
8c What is the risk for <u>obstructive</u> abnormalities associated with patient age at time of radiation?	Weiner 2006 (18)	30 CSS (Wilms tumor, Hodgkin disease, Sarcoma, Hepato-blastoma)	Median 2.79 (range 0-13.7)	100% (n=30)	No correlation between severity of abnormal FEV1 (z-score) and age at time of radiation: - FEV1 z-score (n=30)	Spearman Correlation: No correlation with age at time of radiation r^2<0.001 (very weak)	1. No 2. Yes: Wang X, Pediatr Pulmonol, 1993; Rosenthal M, Thorax 1993 3. No 4. Yes 5. No 6. No	Retrospective cohort SB: High Risk AB: High risk DB: Low risk CF: High Risk
	De 2015 (12)	49 Osteo-sarcoma	Median 2.91 (range 0.01-8.28)	100% (n=49)	Proportion of CCS with abnormal results per parameter FEV1 <80% pred: 29% (14/49) FEF25–5% <68% pred: 20% (10/49)	Univariable logistic regression analysis with age at radiation (cont.) OR (p-value) 1.03 (NS) 1.09 (NS)	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Wang X, Pediatr Pulmonol, 1993 3. No 4. Yes: ATS 5. No 6. No	Retrospective cohort SB: High Risk AB: High Risk DB: Low risk CF: High Risk
	Khan 2020 (23)	66 CCS exposed to radiotherapy	Mean 9 years (range, 1-20)	100% (n=66)	<5 years >5 or <13 years >13 years: 1.0 (ref) <5 years >5 or <13 years >13 years: 1.0 (ref) <5 years >5 or <13 years >13 years: 1.0 (ref)	Multivariable logistic regression, crude model OR (95%CI) 3.20 (0.24-42.19) (NS) 1.68 (0.22-12.96) (NS) Multivariable logistic regression, adjusted for time since treatment OR (95%CI) 11.35 (0.20-634.6) (NS) 2.10 (0.26-16.98) (NS) Multivariable logistic regression, adjusted for time since treatment and bleomycin exposure OR (95%CI) 6.57 (0.08-571.7) (NS) 1.44 (0.11-19.21) (NS)	1. No 2. Yes Rosenthal M, Thorax, 1993 3. No 4. Yes: ATS 5. No 6. No	Retrospective cohort SB: High Risk AB: Low Risk DB: Low risk CF: Low Risk
GRADE assessment: <u>Study design:</u>	+4	3 retrospective cohort studies						

Study limitations:	-3	Important limitations: Selection bias high in 3/3; Attrition bias high in 2/3; Detection bias low in 3/3; Confounding high in 2/3
Consistency:	0	No inconsistency. Two studies show no correlation and non-significant association between obstructive abnormalities and age at radiotherapy. One study shows an increased risk with younger age at radiotherapy, but the associations were not significant and confidence intervals very large.
Directness:	0	Results broadly generalizable for CCS treated with radiotherapy exposing lung tissue. PFT quality is good (3/3 report reference values and guidelines used)
Precision:	-1	Important imprecision; 1/3 reports correlation coefficient only, 1/3 studies shows effect size but without 95%CI and p-value not significant, 1/3 studies shows 95%CI which are very large and not significant
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No age-respnce relationship
Plausible confounding:	0	No evidence of possible confounding
Quality of evidence:	⨁⊖⊖⊖ Very low	
Conclusion:	No significant effect for obstructive abnormalities (FEV1, FEF25-75%) of older vs. younger age at radiotherapy exposing lung tissue in CAYA cancer survivors. (3 studies; 145 participants; 145 participants exposed to radiotherapy exposing lung tissue)	
Comment	Important imprecision	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Radiotherapy exposing lung tissue	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
8c What is the risk for restrictive abnormalities associated with patient age at time of radiation?	Weiner 2006 (18)	30 CSS (Wilms tumor, Hodgkin disease, Sarcoma, Hepato-blastoma)	Median 2.79 (range 0-13.7)	100% (n=30)	No correlation between severity of abnormal TCL (z-score) and age at time of radiation: -TLC z-score (n=23)	Spearman Correlation: No correlation with age at time of radiation r^2=0.08 (very weak)	1. No 2. Yes: Wang X, Pediatr Pulmonol, 1993; Rosenthal M, Thorax 1993 3. No 4. Yes 5. No 6. No	Retrospective cohort SB: High Risk AB: High risk DB: Low risk CF: High Risk
	De 2015 (12)	49 Osteo-sarcoma	Median 2.91 (range 0.01-8.28)	100% (n=49)	Proportion of CCS with abnormal results per parameter FVC <80% pred: 24% (12/49) TLC <77% pred: 15% (7/49)	Univariable logistic regression analysis with age at radiation (cont.) OR (p-value) 1.13 (NS) 1.14 (NS)	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Wang X, Pediatr Pulmonol, 1993 3. No 4. Yes: ATS 5. No 6. No	Retrospective cohort SB: High Risk AB: High Risk DB: Low risk CF: High Risk
	Khan 2020 (23)	66 CCS exposed to radiotherapy	Mean 9 years (range, 1-20)	100% (n=66)	<5 years >5 or <13 years >13 years: 1.0 (ref)	Multivariable logistic regression, crude model OR (95%CI) 3.75 (0.51-27.50) (NS) 2.34 (0.55-9.97) (NS)	1. No 2. Yes Rosenthal M, Thorax, 1993 3. No 4. Yes: ATS 5. No 6. No	Retrospective cohort SB: High Risk AB: Low Risk DB: Low risk CF: Low Risk

					<5 years >5 or <13 years >13 years: 1.0 (ref)	Multivariable logistic regression, adjusted for time since treatment OR (95%CI) 2.22 (0.15-33.44) (NS) 2.06 (0.45-9.51) (NS)		
					<5 years >5 or <13 years >13 years: 1.0 (ref)	Multivariable logistic regression, adjusted for time since treatment and bleomycin exposure OR (95%CI) 1.26 (0.06-25.63) (NS) 1.30 (0.19-8.72) (NS)		

GRADE assessment:		
Study design:	+4	3 retrospective cohort studies
Study limitations:	-3	Important limitations: Selection bias high in 3/3; Attrition bias high in 2/3; Detection bias low in 3/3; Confounding high in 2/3
Consistency:	0	No inconsistency. Two studies show no correlation and non-significant association between restrictive abnormalities and age at radiotherapy. One study shows an increased risk with younger age at radiotherapy, but the associations were not significant and confidence intervals large.
Directness:	0	Results broadly generalizable for CCS treated with radiotherapy exposing lung tissue. PFT quality is good (3/3 report reference values and guidelines used)
Precision:	-1	Important imprecision; 1/2 reports correlation coefficient only, 1/2 studies shows effect size but without 95%CI and p-value not significant, 1/3 studies shows 95%CI which are large and not significant
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No age-respnce relationship
Plausible confounding:	0	No evidence of possible confounding
Quality of evidence:	⊕⊖⊖⊖ Very low	
Conclusion:	No significant effect for restrictive abnormalities (TLC, FVC) of older vs. younger age at radiotherapy exposing lung tissue in CAYA cancer survivors. (3 studies; 145 participants; 145 participants exposed to radiotherapy exposing lung tissue)	
Comment	Important imprecision	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Radiotherapy exposing lung tissue	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
8c What is the risk for hyperinflation associated with patient age at time of radiation?	De 2015 (12)	49 Osteo-sarcoma	Median 2.91 (range 0.01-8.28)	100% (n=49)	Proportion of CCS with abnormal RV/TLC RV/TLC >123% pred: 21% (12/49)	Univariable logistic regression analysis with age at radiation (cont.) OR (p-value) 1.05 (NS)	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Wang X, Pediatr Pulmonol, 1993 3. No 4. Yes: ATS 5. No 6. No	Retrospective cohort SB: High Risk AB: High Risk DB: Low risk CF: High Risk
GRADE assessment:								

Study design:	+4	1 retrospective cohort study
Study limitations:	-3	Important limitations: Selection bias high in 1/1; Attrition bias high in 1/1; Detection bias low in 1/1; Confounding high in 1/1
Consistency:	0	One study only
Directness:	0	Results and outcomes broadly generalizable. PFT quality is good (reference values and guidelines stated).
Precision:	0	Imprecision 1/1 reports OR without 95%CI and p-value is not significant
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No clear relation with increase in the outcome with older age at time of radiotherapy
Plausible confounding:	0	No evidence of possible confounding
Quality of evidence:	⊕⊖⊖⊖ Very low	
Conclusion:	No significant effect on hyperinflation of older vs. younger age at radiotherapy exposing lung tissue in CAYA cancer survivors. (1 study; 49 participants, 49 participants exposed to radiotherapy exposing the lung tissue)	
Comment	Small sample size and important imprecision	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Radiotherapy exposing lung tissue	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
8c What is the risk for diffusion capacity impairment associated with patient age at time of radiation?	Weiner 2006 (18)	30 CSS (Wilms tumor, Hodgkin disease, Sarcoma, Hepato-blastoma)	Median 2.79 (range 0-13.7)	100% (n=30)	No correlation between severity of abnormal DLCO (z-score) and age at time of radiation: - DLCO z-score (n=21)	Spearman Correlation: No correlation with age at time of radiation r^2=0.08 (very weak)	1. No 2. Yes: Wang X, Pediatr Pulmonol, 1993; Rosenthal M, Thorax 1993 3. No 4. Yes 5. No 6. No	Retrospective cohort SB: High Risk AB: High risk DB: Low risk CF: High Risk
	De 2015 (12)	49 Osteo-sarcoma	Median 2.91 (range 0.01-8.28)	100% (n=49)	Proportion of CCS with abnormal results per parameter DLCO adj <65% pred: 9% (4/49)	Univariable logistic regression analysis with age at radiation (cont.) OR (p-value) 1.01 (NS)	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Wang X, Pediatr Pulmonol, 1993 3. No 4. Yes: ATS 5. No 6. No	Retrospective cohort SB: High Risk AB: High Risk DB: Low risk CF: High Risk
	Khan 2020 (23)	66 CCS exposed to radiotherapy	Mean 9 years (range, 1-20)	100% (n=66)	<5 years >5 or <13 years >13 years: 1.0 (ref) <5 years	Multivariable logistic regression, crude model OR (95%CI) 3.75 (0.51-27.5) 3.00 (0.73-12.27) Multivariable logistic regression, adjusted for time since treatment OR (95%CI) 4.27 (0.28-64.08)	1. No 2. Yes Rosenthal M, Thorax, 1993 3. No 4. Yes: ATS 5. No 6. No	Retrospective cohort SB: High Risk AB: Low Risk DB: Low risk CF: Low Risk

				>5 or <13 years >13 years: 1.0 (ref)	3.09(0.71-13.45)		
					Multivariable logistic regression, adjusted for time since treatment and bleomycin exposure OR (95%CI)		
				<5 years >5 or <13 years >13 years: 1.0 (ref)	3.64 (0.18-72.86) 2.74 (0.46-16.18)		

GRADE assessment:		
Study design:	+4	3 retrospective cohort studies
Study limitations:	-3	Important limitations: Selection bias high in 3/3; Attrition bias high in 2/3; Detection bias low in 3/3; Confounding high in 2/3
Consistency:	0	No inconsistency. Two studies show no correlation and non-significant association between diffusion capacity impairment and age at radiotherapy. One study shows an increased risk with younger age at radiotherapy, but the associations were not significant and confidence intervals very large.
Directness:	0	Results broadly generalizable for CCS treated with radiotherapy exposing lung tissue. PFT quality is good (2/2 report reference values and guidelines used)
Precision:	-1	Important imprecision; 1/3 reports correlation coefficient only, 1/3 studies shows effect size but without 95%CI and p-value not significant, 1/3 studies shows 95%CI which are very large and not significant
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No clear relation with increase in the outcome with older age at time of radiotherapy
Plausible confounding:	0	No evidence of possible confounding
Quality of evidence:	⊕⊖⊖⊖ Very low	
Conclusion:	No significant effect on diffusion capacity impairment (DLCO) of older vs. younger age at radiotherapy exposing lung tissue in CAYA cancer survivors. (3 studies; 145 participants; 145 participants exposed to radiotherapy to the thorax)	
Comment	Important imprecision	

8d Radiosensitizer

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Radiotherapy exposing lung tissue	Pulmonary function Outcomes	Effect size	Risk of bias
8d What is the risk of pulmonary dysfunction in CAYA treated with radiosensitizing/radiomimetic chemotherapy (doxorubicin, dactinomycin, busulfan, bleomycin, topotecan, irinotecan) combined with radiotherapy involving lung tissue compared to CAYA not treated with radiomimetic chemotherapy combined with radiotherapy involving lung tissue? → No study							

PICO 9: Thoracic surgery

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Thoracic Surgery	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
9 What is the risk of <u>obstructive</u> abnormalities in CAYA treated with thoracic surgery compared to CAYA not treated with thoracic surgery?	Record 2016 (1)	143 CCS	Mean 14.1 ± 4.8 (SD)	16.8% (n=24)	Obstructive (FVC, FEV1, FEV1/FVC <80% or FEF25–75% <68% predicted) 50.0% (12/24) surgery 21.0% (25/119) no surgery	Univariable comparison Chi2 surgery Yes/No 0.06	1. No 2. Yes: Wang X, Pediatr Pulmonol 2005; Hankinson JL, Am J Respir Crit Care Med 1999 3. No 4. Yes 5. No 6. Yes	Retrospective cohort SB: High risk AB: Low risk DB: Low risk CF: High risk
	De 2015 (12)	49 Osteo-sarcoma	Median 2.91 (range 0.01-8.28)	18% (n=9)	Proportion of CCS with abnormal results per parameter FEV1 <80% pred: 29% (12/49) FEF25–75% <68% pred: 20% (10/49) Obstructive (FEV1/FVC <80%, FEV1<80% or FEF25-75<68% with normal TLC): 24% (12/49)	Logistic regression analysis with surgery yes/no Odds Ratio (p-value) 8.0 (<0.01) 2.35 (NS) 5.89 (<0.05)	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Wang X, Pediatr Pulmonol, 1993 3. No 4. Yes: ATS 5. No 6. No	Retrospective cohort SB: High Risk AB: High Risk DB: Low risk CF: High Risk
	Denbo, 2014 (13)	21 Osteo-sarcoma	Mean 20 yr (SD ±9)	N=15 with 1 Thoracotomy N=6 with ≥2 Thoracotomy	Proportion of CCS with abnormal results per parameter FEV1 <80% pred 1 Thoracotomy (6/15) vs ≥2 Thoracotomies (4/6)	Fishers exact test p-value 0.362	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Miller A, Am Rev Respir Dis, 1983 3. No 4. Yes: ATS, Morris AH, 1984 5. No 6. No	Prospective cohort SB: Low risk AB: Low risk DB: Unclear CF: High risk
	Stone 2020 (19)	62 high-risk neuroblastoma	Median 5.29 (0.24-15.24)	23% (n=14)	**FEV1** (FEV1 <80% pred) Surgery yes: 85.7% abnormal Surgery no: 35.4% abnormal	OR, 95%CI 10.94 (2.19 – 54.71), p=0.001	1. No 2. Yes 3. No 4. Yes (ATS) 5. No 6. No	Prospective cohort SB: high risk AB: low risk DB: low risk CF: high risk

GRADE assessment:		
Study design:	+4	2 retrospective cohort studies, 2 prospective cohort studies
Study limitations:	-2	Some limitations: Selection bias high in 3/4, low in 1/4; Attrition bias high in 1/4, low in 3/4; Detection bias low in 3/4, unclear in 1/4; Confounding high in 4/4
Consistency:	0	No important inconsistency. Most studies show generally worse pulmonary outcomes after thoracic surgery, 2 studies significant results but one with large 95%CI
Directness:	0	Population and outcomes are generalizable. PFT quality is good (4/4 state references and guidelines used).
Precision:	-1	Important imprecision; in 2/4 studies precision cannot be judged as results are shown as p-values only, 1/4 studies shows results as Odds Ration but without 95%CI, 1/4 studies with Odds Ratio but large 95%CI
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	One study shows non-significantly higher proportion of obstructive abnormalities after ≥2 thoracotomies compared to one, but small sample size.
Plausible confounding:	0	No evidence of possible confounding
Quality of evidence:	⊕⊖⊖⊖ Very low	
Conclusion:	Increased risk for obstructive abnormalities (FEV1, FEV1/FVC, FEF25-75, "obstructive") after thoracic surgery vs. no surgery in CAYA cancer survivors. But 3/4 with selected survivor cohorts (osteosarcoma, neuroblastoma) (4 studies; 2 studies significant, 2 studies non-significant; 275 participants; 68 exposed to thoracic surgery to the lung or thorax)	
Comment	Only small sample size exposed to thoracic surgery and effect size either without confidence interval or not assessable as results shown as p-value only.	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Thoracic Surgery	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
9 What is the risk of restrictive abnormalities in CAYA treated with thoracic surgery compared to CAYA not treated with thoracic surgery?	Record 2016 (1)	143 CCS	Mean 14.1 ± 4.8 (SD)	16.8% (n=24)	Restrictive (TLC<80% predicted) 8.3% (2/24) surgery 14.3% (17/119) no surgery	Univariable comparison Chi2 surgery Yes/No 0.01	1. No 2. Yes: Wang X, Pediatr Pulmonol 2005; Hankinson JL, Am J Respir Crit Care Med 1999 3. No 4. Yes 5. No 6. Yes	Retrospective cohort SB: high risk AB: low risk DB: low risk CF: high risk
	De 2015 (12)	49 Osteo-sarcoma	Median 2.91 (range 0.01-8.28)	18% (n=9)	Proportion of CCS with abnormal results per parameter FVC <80% pred: 24% (12/49) TLC <77% pred: 15% 7/49) Restrictive (TLC <77%): 15% (7/49)	Logistic regression with surgery yes/no Odds Ratio (p-value) 3.2 (NS) 1.94 (NS) 1.94 (NS)	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Wang X, Pediatr Pulmonol, 1993 3. No 4. Yes: ATS 5. No 6. No	Retrospective cohort SB: High Risk AB: High Risk DB: Low risk CF: High Risk

	Denbo, 2014 (13)	21 Osteo-sarcoma	Mean 20 yr (SD ±9)	N=15 with 1 thoracotomy N=6 with ≥2 thoracotomies	Proportion of CCS with abnormal results per parameter FVC <80% pred 1 Thoracotomy (5/15) vs ≥2 Thoracotomies (3/5) TLC <75% pred 1 Thoracotomy (2/15) vs ≥2 Thoracotomies (4/6)	Fishers exact test p-value 0.347 0.031	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Miller A, Am Rev Respir Dis, 1983 3. No 4. Yes: ATS, Morris AH, 1984 5. No 6. No	Prospective cohort SB: low risk AB: low risk DB: unclear CF: high risk
	Mulder 2011 (9)	193 CCS	Median 17.9 (5.6-36.8)	16.6% (n=32)	 34/193 Restrictive (TLC OR FVC <75%) Of those Exposed: 7.7%	Odds Ratio (95%CI) for surgery yes/no 3.79 (1.25-11.50)	1. No 2. No 3. No 4. No 5. No 6. No	Retrospective cohort SB: low risk AB: low risk DB: unclear CF: low risk
	Stone 2020 (19)	62 high-risk neuroblastoma	Median 5.29 (0.24-15.24)	23% (n=14)	**FVC** (FVC <80% pred) Surgery yes: 92.9% abnormal Surgery no: 41.5% abnormal **TLC** (TLC <80% pred) Surgery yes: 64.3% abnormal Surgery no: 35.4% abnormal	OR, 95%CI 18.20 (2.20 – 150.58), p=0.001 3.28 (0.95 – 11.38), p=0.054	1. No 2. Yes 3. No 4. Yes (ATS) 5. No 6. No	Prospective cohort SB: high risk AB: low risk DB: low risk CF: high risk

GRADE assessment:		
Study design:	+4	3 retrospective cohort studies, 2 prospective cohort study
Study limitations:	-2	Some limitations: Selection bias high in 3/5, low in 2/5; Attrition bias high in 1/5, low in 4/5; Detection bias low in 3/5, unclear in 2/5; Confounding high in 4/5, low in 1/5
Consistency:	0	Most studies show similar results; in one study CAYA cancer survivors without thoracic surgery have more restrictive abnormalities, in remaining 3 studies exposed are more at risk.
Directness:	-1	Results are generalizable. PFT quality is unsure (4/5 state references and guidelines used).
Precision:	-1	Important imprecision; 1/5 shows effect size with OR and 95%CI, 1/5 shows OR but no CI, 1/5 studies with Odds Ratio but large 95%CI, in 2/5 precision cannot be judged as p-value is shown only
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	One studies shows higher proportion of obstructive abnormalities after ≥2 thoracotomies compared to one, but very small sample size.
Plausible confounding:	0	No evidence of possible confounding
Quality of evidence:	⊕⊖⊖⊖ Very low	
Conclusion:	Increased risk for restrictive abnormalities (FVC, TLC, restrictive) in CAYA cancer survivors after thoracic surgery vs. CAYA cancer survivors without thoracic surgery. But 3/5 with selected survivor cohorts (osteosarcoma, neuroblastoma)	

	(5 studies; 3 significant effect, 2 non-significant effect; 468 participants; 100 participants exposed to thoracic surgery)
Comment	Two studies show effect size, three studies show odds ration or p-value only. One study shows a contradictory result. Different definitions and cutoff values used.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Thoracic Surgery	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
9 What is the risk of <u>hyperinflation</u> in CAYA treated with thoracic surgery compared to CAYA not treated with thoracic surgery?	Record 2016 (1)	143 CCS	Mean 14.1 ± 4.8 (SD)	16.8% (n=24)	Hyperinflation (RV >120%predicted or RV/TLC >28% predicted) 58.3% (14/24) surgery 37.8% no (45/119) surgery	Univariable comparison Chi2 surgery Yes/No 0.41	1. No 2. Yes: Wang X, Pediatr Pulmonol 2005; Hankinson JL, Am J Respir Crit Care Med 1999 3. No 4. Yes 5. No 6. Yes	Retrospective cohort SB: high risk AB: low risk DB: low risk CF: high risk
	De 2015 (12)	49 Osteo-sarcoma	Median 2.91 (range 0.01-8.28)	18% (n=9)	Proportion of CCS with abnormal RV/TLC RV/TLC ratio >28%: 21% (10/49)	Logistic regression with surgery yes/no Odds Ratio (p-value) 8.5 (<0.01)	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Wang X, Pediatr Pulmonol, 1993 3. No 4. Yes: ATS 5. No 6. No	Retrospective cohort SB: High Risk AB: High Risk DB: Low risk CF: High Risk

GRADE assessment:		
<u>Study design:</u>	+4	2 retrospective cohort studies
<u>Study limitations:</u>	-3	Important limitations: Selection bias high in 2/2; Attrition bias high in 1/2, low in 1/2; Detection bias low in 2/2; Confounding high in 2/2
<u>Consistency:</u>	0	Studies show generally more hyperinflation in exposed CAYA cancer survivors, some are significant some not
<u>Directness:</u>	0	Results are generalizable. PFT quality is good (2/2 state references and guidelines used).
<u>Precision:</u>	-1	Important imprecision; 1/2 reports odds ration without confidence interval, in 1/2 precision cannot be judged as the result is shown as p-value only
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	0	No large magnitude of effect
<u>Dose-response:</u>	0	Not applicable
<u>Plausible confounding:</u>	0	No evidence of possible confounding
Quality of evidence:	⊕⊖⊖⊖ Very low	
Conclusion:	Inconsistent findings for hyperinflation (RV/TLC, RV) in CAYA cancer survivors after thoracic surgery vs. CAYA cancer survivors without thoracic surgery. (2 studies; 1 significant effect, 1 non-significant effect; 192 participants; 33 participants exposed to thoracic surgery)	
Comment	Significant finding in one of both studies only and very small sample size.	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Thoracic Surgery	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
9 What is the risk of <u>diffusion capacity impairment</u> in CAYA treated with thoracic surgery compared to CAYA not treated with thoracic surgery?	De 2015 (12)	49 Osteo-sarcoma	Median 2.91 (range 0.01-8.28)	18% (n=9)	Proportion of CCS with abnormal DLCO $DLCO_{adj}$ <65% pred: 9% (4/49) Diffusion defect (DLCO <65%): 14% (6/49)	Logistic regression with surgery yes/no Odds Ratio (p-value) 1.89 (NS) 1.07 (NS)	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Wang X, Pediatr Pulmonol, 1993 3. No 4. Yes: ATS 5. No 6. No	Retrospective cohort SB: High Risk AB: High Risk DB: Low risk CF: High Risk
	Denbo, 2014 (13)	21 Osteo-sarcoma	Mean 20 yr (SD ±9)	N=15 with 1 thoracotomy N=6 with ≥2 thoracotomies	Proportion of CCS with abnormal DLCO $DLCO_{corr}$ <75% pred 1 Thoracotomy (7/15) vs ≥2 Thoracotomies (2/4)	Fishers exact test p-value 1.00	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Miller A, Am Rev Respir Dis, 1983 3. No 4. Yes: ATS, Morris AH, 1984 5. No 6. No	Prospective cohort SB: low risk AB: low risk DB: unclear CF: high risk
	Mulder 2011 (9)	193 CCS	Median 17.9 (5.6-36.8)	16.6% (n=32)	85 Diffusion capacity impairment (DLCO <75%) Of those Exposed: 46.2%	Odds Ratio (95%CI) for surgery yes/no 1.98 (0.68-5.75)	1. No 2. No 3. No 4. No 5. No 6. No	Retrospective cohort SB: low risk AB: low risk DB: unclear CF: low risk
	Stone 2020 (19)	62 high-risk neuroblastoma	Median 5.29 (0.24-15.24)	23% (n=14)	**DLCO** (DLCO <80% pred) Surgery yes: 83.3% abnormal Surgery no: 68.2% abnormal	OR, 95%CI 2.33 (0.45 – 12.09), p=0.475	1. No 2. Yes 3. No 4. Yes (ATS) 5. No 6. No	Prospective cohort SB: high risk AB: low risk DB: low risk CF: high risk

GRADE assessment:

<u>Study design:</u>	+4	2 retrospective cohort studies, 2 prospective cohort study
<u>Study limitations:</u>	-2	Some limitations: Selection bias high in 2/4, low in 2/4; Attrition bias high in 1/4, low in 3/4; Detection bias low in 2/4, unclear in 2/4; Confounding high in 3/4, low in 1/4
<u>Consistency:</u>	0	Most studies show similar results
<u>Directness:</u>	-1	Results are generalizable. PFT quality is unsure (3/4 state references and guidelines used).
<u>Precision:</u>	-1	Important imprecision: 2/4 studies show effect size with CI, 1/4 shows effect size (OR) without CI, and in 1/4 precision cannot be judged as result is shown as p-value only; 3/4 show univariable analysis only

Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Not applicable
Plausible confounding:	0	No evidence of possible confounding
Quality of evidence:	⨁⊖⊖⊖ Very low	
Conclusion:	No significant effect on diffusion capacity impairment (DLCO) after thoracic surgery vs. no surgery in CAYA cancer survivors (4 studies; 325 participants; 76 participants exposed to thoracic surgery)	
Comment	Small sample size exposed to thoracic surgery, definition for cutoff values differ between studies, precision unlear.	

9a Different resection volumes

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Thoracic Surgery	Pulmonary function Outcomes	Effect size	Risk of bias
9a What is the risk associated with different resection volumes?							

No study

9b Age at exposure

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Thoracic Surgery	Pulmonary function Outcomes	Effect size	Risk of bias
9b What is the risk in younger compared to older age at thoracic surgery?							

No study

PICO 10: Combinations

10a Thoracic surgery plus chemotherapy

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Thoracic Surgery and chemotherapy	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
10a What is the risk of <u>obstructive</u> abnormalities after thoracic surgery combined with pulmotoxic chemotherapy (bleomycin, CCNU, BCNU, Busulfan, Cyclophosphamide, Methotrexate, Gemcitabine)?								

No study

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Thoracic surgery and chemotherapy	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
10a What is the risk of <u>restrictive</u> abnormalities after thoracic surgery combined with pulmotoxic chemotherapy (bleomycin, CCNU, BCNU, Busulfan, Cyclophosphamide, Methotrexate, Gemcitabine)?	Mulder 2011 (9)	193 CCS	Median 17.9 (5.6-36.8)	Bleomycin plus surgery 1.6% (n=3) Bleomycin only 50.8% (n=98)	Restrictive impairment (TLC OR FVC <75%) Bleomycin only vs Bleomycin + surgery	Odds Ratio (95%CI) Bleomycin plus surgery vs. Bleomycin only Not estimable as no cases in Bleomycin + surgery	1. No 2. No 3. No 4. No 5. No 6. No	Retrospective cohort SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
<u>Study design:</u>	+4	1 retrospective cohort study
<u>Study limitations:</u>	-1	Some limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding, low in 1/1
<u>Consistency:</u>	0	One study only
<u>Directness:</u>	-1	Results are broadly generalizable. PFT quality is unsure (no reference values and guidelines mentioned).
<u>Precision:</u>	0	OR not estimable, one study only
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	0	No large magnitude of effect
<u>Dose-response:</u>	0	Not applicable
<u>Plausible confounding:</u>	0	No evidence of possible confounding
Quality of evidence:		⨁⊖⊖⊖ Very low
Conclusion:		No statement possible on restrictive abnormalities (TLC, FVC) after thoracic surgery combined with bleomycin vs. bleomycin alone in CAYA cancer survivors. (1 study; 193 participants; 3 participants exposed to thoracic surgery and bleomycin; 98 participants exposed to bleomycin only)
Comment		Very small sample size exposed to thoracic surgery and bleomycin, no effect size, PFT quality is unsure.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Thoracic surgery and chemotherapy	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
10a What is the risk of <u>hyperinflation</u> after thoracic surgery combined with pulmotoxic chemotherapy (bleomycin, CCNU, BCNU, Busulfan, Cyclophosphamide, Methotrexate, Gemcitabine)?								

No study

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Thoracic surgery and chemotherapy	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
10a What is the risk of <u>diffusion capacity impairment</u> after thoracic surgery combined with pulmotoxic chemotherapy (bleomycin, CCNU, BCNU, Busulfan, Cyclophosphamide, Methotrexate, Gemcitabine)?	Mulder 2011 (9)	193 CCS	Median 17.9 (5.6-36.8)	Bleomycin plus surgery 1.6% (n=3) Bleomycin only 50.8% (n=98)	Diffusion capacity impairment (DLCO <75%) Bleomycin only vs Bleomycin + surgery	Odds Ratio (95%CI) Bleomycin plus surgery vs. Bleomycin only 1.38 (0.10-18.66)	1. No 2. No 3. No 4. No 5. No 6. No	Retrospective cohort SB: low risk AB: low risk DB: unclear CF: low risk
GRADE assessment:								
<u>Study design:</u>	+4	1 retrospective cohort study						
<u>Study limitations:</u>	-1	Some limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1; Confounding, low in 1/1						
<u>Consistency:</u>	0	One study only						
<u>Directness:</u>	-1	Results are broadly generalizable. PFT quality is unsure (no reference values and guidelines mentioned).						
<u>Precision:</u>	-2	Results shown with effect size but large confidence interval, one study only						
<u>Publication bias:</u>	0	Unlikely						
<u>Effect size:</u>	0	No large magnitude of effect						
<u>Dose-response:</u>	0	Not applicable						
<u>Plausible confounding:</u>	0	No evidence of possible confounding						
Quality of evidence:	⊕⊖⊖⊖ Very low							
Conclusion:	No significant effect on diffusion capacity impairment (DLCO) after thoracic surgery combined with bleomycin vs. bleomycin alone in CAYA cancer survivors in one study. (1 study; 193 participants; 3 participants exposed to thoracic surgery and bleomycin; 98 participants exposed to bleomycin only)							
Comment	Very small sample size exposed to thoracic surgery and bleomycin, large confidence interval, PFT quality is unsure.							

10b Thoracic surgery plus radiotherapy

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Thoracic surgery and radiotherapy	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
10b What is the risk of <u>obstructive abnormalities</u> after thoracic surgery combined with	Stone 2020 (19)	62 high-risk neuroblastoma	Median 5.29 (0.24-15.24)	18% (n=12)	**FEV1** (FEV1 <80% pred) RT + Surgery yes: 91.7% abnormal RT + Surgery no: 36% abnormal	OR, 95%CI 19.56 (2.33 – 164.05), p=0.001	1. No 2. Yes 3. No 4. Yes (ATS) 5. No 6. No	Prospective cohort SB: high risk AB: low risk DB: low risk CF: high risk

radiotherapy exposing lung tissue?		
GRADE assessment:		
Study design:	+4	1 prospective 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 high in 1/1
Consistency:	0	One study only
Directness:	0	Results are broadly generalizable. PFT quality is good (reference values and guidelines mentioned).
Precision:	-2	Results shown with effect size but very large confidence interval, one study only
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect
Dose-response:	0	Not applicable
Plausible confounding:	0	No evidence of possible confounding
Quality of evidence:	⨁⊖⊖⊖ VERY LOW	
Conclusion:	Increased risk for obstructive abnormalities (FEV1) after thoracic surgery combined with radiotherapy exposing lung tissue vs. no exposure in CAYA cancer survivors. (1 study; 62 participants; 12 participants exposed to radiotherapy exposing lung tissue plus thoracic surgery; 51 participants not exposed)	
Comment	One study, very small sample size exposed to thoracic surgery and radiotherapy exposing lung tissue, very large confidence interval.	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Thoracic surgery and radiotherapy	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
10b What is the risk of <u>restrictive abnormalities</u> after thoracic surgery combined with radiotherapy exposing lung tissue?	Mulder 2011 (9)	193 CCS	Median 17.9 (5.6-36.8)	Radiotherapy plus surgery 8.3% (n=16) Bleomycin only 50.8% (n=98)	Restrictive impairment (TLC OR FVC <75%) Bleomycin only vs radiotherapy + surgery	Odds Ratio (95%CI) Radiotherapy plus surgery vs. Bleomycin only 33.44 (7.81-143.09)	1. No 2. No 3. No 4. No 5. No 6. No	Retrospective cohort SB: low risk AB: low risk DB: unclear CF: low risk
	Stone 2020 (19)	62 high-risk neuroblastoma	Median 5.29 (0.24-15.24)	18% (n=12)	**FVC** (FVC <80% pred) RT + Surgery yes: 91.7% abnormal RT + Surgery no: 44% abnormal **TLC** (TLC <80% pred) RT + Surgery yes: 75.0% abnormal RT + Surgery no: 34.0% abnormal	OR, 95%CI 14.00 (1.68 – 116.85), p=0.003 5.82 (1.39 – 24.38), p=0.010	1. No 2. Yes 3. No 4. Yes (ATS) 5. No 6. No	Prospective cohort SB: high risk AB: low risk DB: low risk CF: high risk

GRADE assessment:		
<u>Study design:</u>	+4	1 retrospective cohort study, 1 prospective cohort study
<u>Study limitations:</u>	-1	Some limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 2/2; Detection bias low in 1/2, unclear in 1/2; Confounding high in 1/2low in 1/2
<u>Consistency:</u>	0	Both studies show an increased risk
<u>Directness:</u>	-1	Results are broadly generalizable. PFT quality differs (1/2 reference values and guidelines mentioned).
<u>Precision:</u>	-1	Results shown with effect size but very large confidence intervals
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	+1	Large magnitude of effect
<u>Dose-response:</u>	0	Not applicable
<u>Plausible confounding:</u>	0	No evidence of possible confounding

Quality of evidence:	⊕⊖⊖⊖ VERY LOW
Conclusion:	Increased risk for restrictive abnormalities (TLC, FVC) after thoracic surgery combined with radiotherapy exposing lung tissue vs. bleomycin alone or no exposure to thoracic surgery and radiotherapy exposing lung tissue in CAYA cancer survivors. (2 studies; 255 participants; 28 participants exposed to radiotherapy exposing lung tissue plus thoracic surgery; 98 participants exposed to bleomycin only or 50 not exposed)
Comment	Two study, very small sample size exposed to thoracic surgery and radiotherapy exposing lung tissue, very large confidence interval. Different comparators used.

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Thoracic surgery and radiotherapy	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
10b What is the risk of <u>hyperinflation</u> after thoracic surgery combined with radiotherapy exposing lung tissue?								
No study								

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Thoracic surgery and radiotherapy	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
10b What is the risk of <u>diffusion capacity impairment</u> after thoracic surgery combined with radiotherapy exposing lung tissue?	Mulder 2011 (9)	193 CCS	Median 17.9 (5.6-36.8)	Radiotherapy plus surgery 8.3% (n=16) Bleomycin only 50.8% (n=98)	Impaired diffusion (DLCO <75%) Bleomycin only vs radiotherapy + surgery	Odds Ratio (95%CI) Radiotherapy plus surgery vs. Bleomycin only 5.98 (1.64-21.81)	1. No 2. No 3. No 4. No 5. No 6. No	Retrospective cohort SB: low risk AB: low risk DB: unclear CF: low risk
	Stone 2020 (19)	62 high-risk neuroblastoma	Median 5.29 (0.24-15.24)	18% (n=12)	**DLCO** (DLCO <80% pred) RT + Surgery yes: 80.0% abnormal RT + Surgery no: 69.6% abnormal	OR, 95%CI 1.75 (0.33 – 9.31), p=0.70	1. No 2. Yes 3. No 4. Yes (ATS) 5. No 6. No	Prospective cohort SB: high risk AB: low risk DB: low risk CF: high risk

GRADE assessment:		
<u>Study design:</u>	+4	1 retrospective cohort study, 1 prospective cohort study
<u>Study limitations:</u>	-1	Some limitations: Selection bias low in 1/2, high in 1/2; Attrition bias low in 2/2; Detection bias low in 1/2, unclear in 1/2; Confounding, low in 1/2, high in 1/2
<u>Consistency:</u>	0	Both studies show an increased risk, one with a significant effect
<u>Directness:</u>	-1	Results are broadly generalizable. PFT quality differs (1/2 reference values and guidelines mentioned).
<u>Precision:</u>	-1	Results shown with effect size but large confidence interval
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	+1	Large magnitude of effect
<u>Dose-response:</u>	0	Not applicable
<u>Plausible confounding:</u>	0	No evidence of possible confounding
Quality of evidence:	⨁⊖⊖⊖ VERY LOW	
Conclusion:	Increased risk for diffusion capacity impairment (DLCO) after thoracic surgery combined with radiotherapy exposing lung tissue vs. bleomycin alone or no exposure to thoracic surgery and radiotherapy exposing lung tissue in CAYA cancer survivors (2 studies; 255 participants; 28 participants exposed to radiotherapy exposing lung tissue and thoracic surgery; 98 participants exposed to bleomycin only, 50 not exposed to thoracic surgery and radiotherapy exposing lung tissue)	
Comment	Very small sample size exposed to thoracic surgery and radiotherapy exposing lung tissue, very large confidence intervals.	

10c Chemo plus radiotherapy

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy and radiotherapy	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
10c What is the risk of <u>obstructive abnormalities</u> after pulmotoxic chemotherapy combined with radiotherapy exposing lung tissue?	Nysom 1998 (24)	41 Lymphoma survivors	Median 10.5 (range 2.3-23.7)	51% (n=21) chemo plus thoracic radiation 49% (n=20) chemo only	Number of CCS with abnormal FEV1 (z-score <-1.645 or >1.645) 11/41 total abnormal FEV1	Estimated difference in z-score for FEV1 (p-value) Chemo plus radiotherapy vs. chemo only 0.8 (0.004)	1. No 2. Yes Quanjer 1983 and 1995, Rosenthal 1993 3. Yes 4. Yes 5. No 6. No	Retrospective cohort SB: Low risk AB: Low risk DB: High risk CF: High risk

GRADE assessment:		
<u>Study design:</u>	+4	1 retrospective cohort study
<u>Study limitations:</u>	-2	Some limitations: Selection bias low in 1/1; Attrition bias low in 1/1; Detection bias high in 1/1; Confounding high in 1/3
<u>Consistency:</u>	0	One study only
<u>Directness:</u>	0	Results generalizable. PFT quality is good (reference values and guidelines mentioned).
<u>Precision:</u>	-2	Important imprecision; only one study and small sample size
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	0	No large magnitude of effect
<u>Dose-response:</u>	0	Not applicable
<u>Plausible confounding:</u>	0	No evidence of possible confounding
Quality of evidence:	⊕⊖⊖⊖ Very low	
Conclusion:	Decreased risk for obstructive abnormalities (FEV1) after radiotherapy exposing lung tissue combined with chemotherapy vs. chemotherapy alone in CAYA cancer survivors (1 study; 41 participants; 21 participants exposed to chemotherapy and radiotherapy exposing lung tissue ; 20 participants exposed to chemotherapy only)	
Comment	One study only, small sample size, univariable analysis only	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy and radiotherapy exposing lung tissue	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
10c What is the risk of <u>restrictive</u> abnormalities after pulmotoxic chemotherapy combined with radiotherapy	Nysom 1998 (20)	41 Lymphoma survivors	Median 10.5 (range 2.3-23.7)	51% (n=21) chemo plus thoracic radiation 49% (n=20) chemo only	Number of CCS with abnormal lung function parameter Total 16/41 restrictive flow volume curve: chemo+RT vs chemo	p-value 0.4	1. No 2. Yes Quanjer 1983 and 1995, Rosenthal 1993 3. Yes 4. Yes 5. No 6. No	Retrospective cohort SB: Low risk AB: Low risk DB: High risk CF: High risk

exposing lung tissue?	Mulder 2011 (9)	193 CCS	Median 17.9 (5.6-36.8)	Bleomycin only 50.8% (n=98) Bleomycin plus radiotherapy 4.7% (n=9)	Restrictive impairment (TLC OR FVC <75%)	Odds Ratio (95%CI) Radiotherapy plus bleomycin vs. Bleomycin only 9.41 (1.71-51.86)	1. No 2. No 3. No 4. No 5. No 6. No	Retrospective cohort SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	2 retrospective cohort studies
Study limitations:	-2	Some limitations: Selection bias low in 2/2; Attrition bias low in 2/2; Detection bias high in 1/2, unclear in 1/2; Confounding high in 1/2, low in 1/2
Consistency:	0	Both studies show tendency to restrictive abnormalities
Directness:	-1	Results broadly generalizable but unsure PFT quality (1/2 stated reference values, ½ stated lung function procedure used)
Precision:	-1	Important imprecision, 1/2 with very wide confidence interval, in 1/2 precision cannot be judged as result shown as p-value only
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect
Dose-response:	0	Not applicable
Plausible confounding:	0	No evidence of possible confounding
Quality of evidence:	⨁⊖⊖⊖ Very low	
Conclusion:	Increased risk for restrictive abnormalities (TLC or FVC) after radiotherapy exposing lung tissue combined with bleomycin vs. bleomycin alone in CAYA cancer survivors (2 studies; 1 study significant, 1 study non-significant; 234 participants; 30 participants exposed to chemotherapy and radiotherapy exposing lung tissue)	
Comment	Important imprecision, PFT quality unsure, small sample size exposed to chemotherapy and radiotherapy exposing lung tissue; one study focusses on bleoymcin-containing chemotherapy the second does not differentiate between type of chemotherapy	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy and radiotherapy	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
10c What is the risk of hyperinflation after pulmotoxic chemotherapy combined with radiotherapy to the chest?								

No stud y

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Chemotherapy and radiotherapy	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
10c What is the risk of diffusion capacity impairment after pulmotoxic chemotherapy combined with radiotherapy to the chest?	Nysom 1998 (20)	41 Lymphoma survivors	Median 10.5 (range 2.3-23.7)	51% (n=21) chemo plus thoracic radiation 49% (n=20) chemo only	Number of CCS with abnormal transfer factor Total 16/41 abnormal transfer factor:	Estimated difference in standardized residuals (p-value) Chemo+RT vs chemo alone 0.1 (0.7)	1. No 2. Yes Quanjer 1983 and 1995, Rosenthal 1993 3. Yes 4. Yes 5. No 6. No	Retrospective cohort SB: Low risk AB: Low risk DB: High risk CF: High risk

	Mulder 2011 (9)	193 CCS	Median 17.9 (5.6-36.8)	Bleomycin only 50.8% (n=98) Bleomycin plus radiotherapy 4.7% (n=9)	Diffusion impairment (DLCO <75%)	Odds Ratio (95%CI) Bleomycin only vs radiotherapy + bleomycin 6.17 (1.37-27.84)	1. No 2. No 3. No 4. No 5. No 6. No	Retrospective cohort SB: low risk AB: low risk DB: unclear CF: low risk
GRADE assessment:								
Study design:	+4	2 retrospective cohort studies						
Study limitations:	-2	Some limitations: Selection bias low in 2/2; Attrition bias low in 2/2; Detection bias high in 1/2, unclear in 1/2; Confounding high in 1/2, low in ½						
Consistency:	0	Both studies show tendency to diffusion capacity impairment						
Directness:	-1	Results broadly generalizable but unsure PFT quality (1/2 stated reference values, ½ stated lung function procedure used)						
Precision:	-1	Important imprecision, 1/2 with very wide confidence interval, in 1/2 precision cannot be judged as result shown as p-value only						
Publication bias:	0	Unlikely						
Effect size:	+1	Large magnitude of effect						
Dose-response:	0	Not applicable						
Plausible confounding:	0	No evidence of possible confounding						
Quality of evidence:	⨁⊖⊖⊖ Very low							
Conclusion:	Increased risk for diffusion capacity impairment abnormalities after radiotherapy exposing lung tissue combined with bleomycin vs. bleomycin alone in CAYA cancer survivors. (2 studies; 1 study significant, 1 study non-significant; 234 participants; 30 participants exposed to chemotherapy and radiotherapy)							
Comment	Important imprecision, PFT quality unsure, small sample size exposed to chemotherapy and radiotherapy; one study focusses on bleoymcin-containing chemotherapy the second does not differentiate between type of chemotherapy							

PICO 11: Smoking

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Tobacco exposure	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
11 What is the risk of obstructive abnormalities in CAYA who have a history of tobacco exposure compared to CAYA with no history of tobacco exposure	Stone 2020 (19)	62 high-risk neuroblastoma	Median 5.29 (0.24-15.24)	18% (n=11)	**FEV1** (FEV1 <80% pred) Smoke yes: 36.4% abnormal Smoke no: 49% abnormal	OR, 95%CI 0.59 (0.16 – 2.28), p=0.446	1. No 2. Yes 3. No 4. Yes (ATS) 5. No 6. No	Prospective cohort SB: high risk AB: low risk DB: low risk CF: high risk
GRADE assessment:								

Study design:	+4	1 prospective cohort study
Study limitations:	-2	Some limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding high in 1/1
Consistency:	0	One study only
Directness:	0	Results broadly generalizable. PFT good (references stated, lung function procedure mentioned)
Precision:	-1	No important imprecision (effect size with 95%CI), only one study
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose-response relationship
Plausible confounding:	0	No evidence of possible confounding
Quality of evidence:	⊕⊖⊖⊖ Very low	
Conclusion:	No significant effect on reduced risk for obstructive abnormalities (FEV1) CAYA cancer survivors with a smoking history compared to those without. (1 study; 62 participants; 11 former or current smoker)	
Comment	One study only, small sample size, only neuroblastoma survivors	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Tobacco exposure	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
11 What is the risk of restrictive abnormalities in CAYA who have a history of tobacco exposure compared to CAYA with no history of tobacco exposure	Stone 2020 (19)	62 high-risk neuroblastoma	Median 5.29 (0.24-15.24)	18% (n=11)	**FVC** (FVC <80% pred) Smoke yes: 45.5% abnormal Smoke no: 54.9% abnormal **TLC** (TLC <80% pred) Smoke yes: 36.4% abnormal Smoke no: 43.1% abnormal	OR, 95%CI 0.69 (0.19 – 2.53), p=0.569 0.75 (0.20 – 2.90), p=0.748	1. No 2. Yes 3. No 4. Yes (ATS) 5. No 6. No	Prospective cohort SB: high risk AB: low risk DB: low risk CF: high risk

GRADE assessment:		
Study design:	+4	1 prospective cohort study
Study limitations:	-2	Some limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding high in 1/1
Consistency:	0	One study only
Directness:	0	Results broadly generalizable. PFT good (references stated, lung function procedure mentioned)
Precision:	-1	No important imprecision (effect size with 95%CI), only one study
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose-response relationship
Plausible confounding:	0	No evidence of possible confounding
Quality of evidence:	⊕⊖⊖⊖ Very low	
Conclusion:	No significant effect on reduced risk for obstructive abnormalities (FVC, TLC) CAYA cancer survivors with a smoking history compared to those without. (1 study; 62 participants; 11 former or current smoker)	
Comment	One study only, small sample size, only neuroblastoma survivors	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Tobacco exposure	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
11 What is the risk of hyperinflation in CAYA who have a history of tobacco exposure compared to CAYA with no history of tobacco exposure								

No study

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Tobacco exposure	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
11 What is the risk of diffusion capacity impairment in CAYA who have a history of tobacco exposure compared to CAYA with no history of tobacco exposure	Stone 2020 (19)	62 high-risk neuroblastoma	Median 5.29 (0.24-15.24)	18% (n=11)	**DLCO** (FVC <80% pred) Smoke yes: 54.6% abnormal Smoke no: 75.6% abnormal	OR, 95%CI 0.39 (0.10 – 1.52), p=0.263	1. No 2. Yes 3. No 4. Yes (ATS) 5. No 6. No	Prospective cohort SB: high risk AB: low risk DB: low risk CF: high risk

GRADE assessment:		
Study design:	+4	1 prospective cohort study
Study limitations:	-2	Some limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias low in 1/1; Confounding high in 1/1
Consistency:	0	One study only
Directness:	0	Results broadly generalizable. PFT good (references stated, lung function procedure mentioned)
Precision:	-1	No important imprecision (effect size with 95%CI), only one study
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose-response relationship
Plausible confounding:	0	No evidence of possible confounding
Quality of evidence:	⊕⊖⊖⊖ Very low	
Conclusion:	No significant effect on reduced risk for obstructive abnormalities (DLCO) CAYA cancer survivors with a smoking history compared to those without. (1 study; 62 participants; 11 former or current smoker)	
Comment	One study only, small sample size, only neuroblastoma survivors	

11a Smoker vs ex-smoker

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Tobacco exposure	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias

11a What is the risk of <u>obstructive abnormalities</u> in smokers/ex-smokers compared to non-smokers?	Oancea 2014 (25)	433 CCS	>10 yrs from diagnosis	a. Never Smoker: 62% (n=269) b. Former: 18% (n=80) c. Current: 19% (n=84) d. Ever smoker <6PY (n=69) e. Ever smoker ≥6PY (n=80)	% predicted median (IQR) **FEV1/FVC** a. 1.02 (0.96-1.06) b. 0.98 (0.93-1.04) c. 1.00 (0.94-1.04) d. 1.00 (0.94-1.04) e. 0.99 (0.92-1.03) **FEV1** a. 79.0 (69.0-92.0) b. 76.5 (65.5-86.0) c. 79.5 (67.0-89.0) d. 79.0 (69.0-88.0) e. 78.0 (66.0-87.0)	Comparison with never smoker as ref., using the DSCF procedure p=0.01 p=0.03 p=0.38 p=0.005 p=0.23 p=0.83 p=0.66 p=0.38	1. No 2. No 3. No 4. Yes: ATS 5. No 6. No	Retrospective cohort SB: high risk AB: low risk DB: low risk CF: unclear

GRADE assessment:		
<u>Study design:</u>	+4	1 retrospective cohort study
<u>Study limitations:</u>	-2	Some limitations: Selection bias high in 1/1; Attrition bias high in 1/1; Detection bias low in 1/1; Confounding unclear in 1/1
<u>Consistency:</u>	0	One study only
<u>Directness:</u>	-1	Results broadly generalizable but unsure PFT quality (no references stated, lung function procedure mentioned)
<u>Precision:</u>	-2	Important imprecision, precision cannot be judged because results shown as p-value only, only one study
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	0	No large magnitude of effect
<u>Dose-response:</u>	0	No dose-response relationship
<u>Plausible confounding:</u>	0	No evidence of possible confounding
Quality of evidence:	⊕⊖⊖⊖ Very low	
Conclusion:	Increased risk for obstructive abnormalities (FEV1/FVC) in current and former smoker and those who smoked ≥6 PY vs. never smokers in CAYA cancer survivors. (1 study; 433 participants; 164 former or current smoker)	
Comment	Important imprecision, PFT quality unsure	

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Tobacco exposure	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
11a What is the risk of <u>restrictive abnormalities</u> in smokers/ex-smokers compared to non-smokers?	Oancea 2014 (21)	433 CCS	>10 yrs from diagnosis	a. Never Smoker: 62% (n=269) b. Former: 18% (n=80) c. Current: 19% (n=84) d. Ever smoker <6PY (n=69) e. Ever smoker ≥6PY	% predicted median (IQR) **TLC** a. 80.0% (69-91) b. 82.0% (73-93) c. 87.0% (74-94) d. 81.0% (70-90) e. 86.5% (74-94)	Comparison with never smoker as ref., using the DSCF procedure p=0.54 p=0.12 p=0.98 p=0.08	1. No 2. No 3. No 4. Yes: ATS 5. No 6. No	Retrospective cohort SB: high risk AB: low risk DB: low risk CF: unclear

				(n=80)				
					FVC a. 79.0 (67.0-91.0) b. 77.0 (67.5-88.0) c. 83.0 (70.0-90.0) d. 80.0 (68.0-87.0) e. 81.5 (68.0-88.5)	 p=0.80 p=0.88 p=0.85 p=0.99		
	Nysom 1998 (11)	94 leukemia survivors	Median 10.6 (range 3.4-23.4)	19% smoker (n=18) 4% former smoker (n=4)	15 TLC reduced/raised	Regression coeff. (95%CI, p-value): 0.31 (-0.18 - 0.80, 0.2)	1. No 2. Yes Reference form own laboratory by adjusting published reference values (Quanjer PH, Pediatr Pulmonol. 1995; Rosenthal M, Thorax, 1993; Quanjer PH, Bull Eur Physiopathol Respir, 1983: Stam H, Pediatr Pulmonl, 1996) 3. Yes 4. Yes 5. No 6. No	Prospective cohort SB: High risk AB: Low risk DB: Unclear CF: High risk
	Armenian, 2015 (14)	121 CCS	Median 17.1 (6.3-40.1)	5.0% (n=6)	Total 29 restrictive (TLC <75% and FEV1 ≥80% predicted)	Logistic regression Odds Ratio (95%CI) 0.9 (0.7-1.9)	1. Yes 2. No 3. No 4. Yes: ATS 5. No 6. Yes	Prospective cohort SB: Low risk AB: low risk DB: low risk CF: high risk

GRADE assessment:			
Study design:		+4	1 retrospective cohort studies, 2 prospective cohort studies
Study limitations:		-2	Some limitations: Selection bias high in 2/3, low in 1/3; Attrition bias low in 3/3; Detection bias low in 2/3, unclear in 1/3; Confounding high in 2/3, unclear 1/3
Consistency:		0	All studies show similar results
Directness:		-1	Results broadly generalizable but unsure PFT quality (1/3 stated reference values, 3/3 mention lung function procedure)
Precision:		-1	Important imprecision, 2/3 with small confidence intervals, in 1/3 precision cannot be judged as results are shown as p-values only
Publication bias:		0	Unlikely
Effect size:		0	No large magnitude of effect
Dose-response:	NA	0	No dose-response relationship
Plausible confounding:		0	No evidence of possible confounding
Quality of evidence:			⊕⊖⊖⊖ Very low
Conclusion:			No significant effect on restrictive abnormalities (TLC, FVC, "restrictive") in CAYA cancer survivors who smoke/smoked compared to non-smoker. (3 studies; 648 participants; 182 participants current or former smoker)
Comment			Two studies with very small number of CCS who smoke/smoked. PFT quality is unsure. Different definitions for "restrictive".

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Tobacco exposure	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
11a What is the risk of hyperinflation in smokers/ex-smokers compared to non-smokers?								

No study

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Tobacco exposure	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
11a What is the risk of diffusion capacity impairment in smokers/ex-smokers compared to non-smokers?	Myrdal 2018 (26)	116 ALL	Median 23.2 (range 7.4 – 40.0)	19% (n=22)	DLCO %predicted in CCS smoking vs. non-smoker Total 22% (n=25) DLCO below %pred	Multivariable analysis, Correlation coeff. β (95% CI, p-value -9.8 (-16.0 - -3.6, 0.002)	1. No 2. Yes: Wanger J, Eur Respir J, 2005; Pellegrino R, Eur Respir J, 2005 3. No 4. Yes: ERS 5. No 6. No	Prospective cross-sectional SB: unclear AB: low risk DB: unclear CF: low risk
	Oancea 2014 (21)	433 CCS	>10 yrs from diagnosis	a. Never Smoker: 62% (n=269) b. Former: 18% (n=80) c. Current: 19% (n=84) d. Ever smoker <6PY (n=69) e. Ever smoker ≥6PY (n=80)	% predicted median (IQR) **DLCOcorr** a. 77.5% (66.0-89.0) b. 77.0% (68.6-86.5) c. 74.0% (60.0-82.0) d. 77.5 (64.5-85.0) e. 71.5% (62.0-81.0)	Comparison with never smoker as ref., using the DSCF procedure p=0.99 p=0.02 p=0.96 p=0.03	1. No 2. No 3. No 4. Yes: ATS 5. No 6. No	Retrospective cohort SB: high risk AB: low risk DB: low risk CF: unclear
	Armenian, 2015 (14)	121 CCS	Median 17.1 (6.3-40.1)	5.0% (n=6)	Total 42 diffusion abnormality	Univariable regression Odds Ratio (95%CI) 0.9 (0.2-5.3)	1. Yes 2. No 3. No 4. Yes: ATS 5. No 6. Yes	Prospective cohort SB: Low risk AB: low risk DB: low risk CF: high risk
	Zorzi 2015 (16)	143 CCS (Hodgkin, extracranial germ cell tumor)	Median 4.4 (2 – 7.4)	2% (n=3)	Total 27 abnormal DLCO	p=0.04	1. No 2. Yes Stanojevic S, Am J Respir Crit Care Med, 2008; Wanger J, Eur Respir J, 2005; Weng TR, Am Rev Respir Dis, 1969; Pellegrino R, Eur Respir J, 2005; reference equations from Sick Children 3. No 4. No 5. No 6. No	Retrospective cross-sectional SB: high risk AB: low risk DB: low risk CF: unclear
GRADE assessment: Study design: +4 1 retrospective cohort study, 1 prospective cohort study, 1 prospective cross-sectional study, 1 retrospective cross-sectional study Study limitations: -2 Some limitations: Selection bias high in 2/4, low in 1/4, unclear in 1/4; Attrition bias low in 4/4; Detection bias low in 3/4, unclear in 1/4; Confounding high in 1/4, low in 1/4, unclear 2/4								

Consistency:	0	Most studies show similar results
Directness:	-1	Results broadly generalizable but unsure PFT quality (2/4 stated reference values, 3/4 mention lung function procedure)
Precision:	-1	Important imprecision, 1/4 with small confidence interval, 1/4 with large confidence interval, in 2/4 precision cannot be judged as results are shown as p-value only
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	No dose-response relationship
Plausible confounding:	0	No evidence of possible confounding
Quality of evidence:	⊕⊖⊖⊖ Very low	
Conclusion:	Inconsistent findings for diffusion capacity impairment in CAYA cancer survivors for current smoker and those who ever smoked ≥6py vs. ….?? . (4 studies; 813 participants; 195 exposed to smoking)	
Comment	Two studies with very small sample size exposed to smoking, important imprecision, and PFT quality is unsure.	

11b Different doses

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Tobacco exposure	Pulmonary function Outcomes	Effect size	Risk of bias
11b What is the risk associated with different doses (pack-years)?							

No study

11c Environmental tobacco smoke

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Tobacco exposure	Pulmonary function Outcomes	Effect size	Risk of bias
11c What is the risk in patients exposed to environmental tobacco smoke compared to not exposed?							

No study

11d Marijuana

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Tobacco exposure	Pulmonary function Outcomes	Effect size	Risk of bias
11d.What is the risk in marijuana smokers compared to non-smokers?							

No study