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

PICO 1: Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

			<u> </u>					
PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Allogeneic HSCT n (%)	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
	Record 2016 (1)	5 143 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:								
Study design:	+4		•					
Study limitations:	-2			h in 1/1; Attrition bi	as low in 1/1; Detection bias l	ow in 1/1; Confounding	g high in 1/1	
Consistency:	C							
<u>Directness:</u>	-1		ect, population and o g function data desc		neralizable; PFT quality unsur	e (no control group me	ntioned, no quality che	ecks performed, no
Precision:	-2	One study only	, univariable compa	rison and no effect n	neasure			
Publication bias:	C	/						
Effect size:	C		sure, only univariable	comparison				
<u>Dose-response:</u>	(	• •						
Plausible confounding			•					
Quality of evidence:		⊖⊖⊖ VERY LOW		/==./4	. /=		6	
Conclusion:		_	on obstructive abnor	malities (FEV1, FEV1	L/FVC <80%pred or FEF25–759	% <68%) in CAYA cancei	r survivors after alloge	neic HSCT vs. no
		ogeneic HSCT.	S		*****			
		,,	ficant effect; 143 par		•			
Comment:	On	ily univariable com	iparison between CC	S exposed to alloger	neic HSCT and not exposed wit	th Chi2 test and no effe	ct 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 restrictive 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
Study design: Study limitations: Consistency: Directness:  Precision: Publication bias: Effect size: Dose-response: Plausible confoundin Quality of evidence Conclusion:	+4 -2 0 -1 -2 0 0 0 0 0 sng: 0 No s	One study only Results are dire cleaning of lung One study only, Unlikely No effect mease Not applicable Only univariable OHO VERY LOW ignificant effect of	s: Selection bias hig ct, population and c function data descr univariable compar ure, only univariable e comparison	outcomes broadly genibed) ison and no effect me comparison	ed) in CAYA cancer survivors	ure (no control group me	ntioned, no quality che	ecks performed, no
Comment:		,, ,		ticipants; 19 restrict S exposed to allogen	ive) eic HSCT and not exposed w	vith Chi2 test and no effe	ct 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 hyperinflation 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: Study design:	+4	Retrospective c	ohort study					
Study limitations:	-2	Some limitation	•	h in 1/1; Attrition bia	s low in 1/1; Detection bias	low in 1/1; Confounding	high in 1/1	
Consistency:	0	One study only			and the black of the control	/	at a seal or a second tax calculation	-l
<u>Directness:</u>	-1		ct, population and c function data desci		neralizable; PFT quality unsu	are (no control group mer	itioned, no quality che	cks performed, no
Precision:	-2			ison and no effect m	easure			
Publication bias:	0	Unlikely	,					
Effect size:	0	No effect measi	ure, only univariable	comparison				
Dose-response:	0	Not applicable						
Plausible confoundi	<u>ng:</u> 0	Only univariable	e comparison					
Quality of evidence	: ⊕∈	⊖⊖ VERY LOW						
Conclusion:	Incre	eased risk for hyp	erinflation (RV >120	%pred or RV/TLC >28	8%pred) in CAYA cancer sur	vivors after allogeneic HS	CT vs. no allogeneic HS	SCT
	(1 st	udy; 1 significant	effect; 143 participa	nts; 59 hyperinflatio	n)			
Comment:	Only	univariable com	parison between CC	S exposed to allogen	eic HSCT and not exposed v	vith Chi2 test and no effec	ct 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 obstructive abnormalities in younger compared to	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 <sub>25%-75%</sub>	Hazard Ratio (p-value) Older age at HSCT continuously, per year	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999 3. No 4. Yes: ATS	Prospective cohort SB: High risk AB: Low risk DB: Low risk CF: Unclear
older age at HSCT?					49% FEF <sub>25%-75%</sub> (<67%pred)	1.082 (0.038)	5. No 6. No	
	Ginsberg, 2010 (3)	317 CCS (PFT post HSCT)	0 - >5 years	241 (76%) Age at HSCT:	Z-score Mean (SD) for FEV1 at last post-transplant test	P-value of ANOVA	<ol> <li>No</li> <li>Yes</li> <li>Rosenthal M, Thorax,</li> </ol>	Retrospective cohort SB: High risk
		133 CCS (PFT pre and		a. <7.8 yr (n=77)	a1.270 (1.495)	0.0790	1993, Hankinson JL, Am J Respir Crit Care Med, 1999	AB: Low risk DB: Low risk
		post HSCT)		b. 7.8 – 11.4 yr (n=79)	b1.862 (1.469)		3. No 4. Yes: ATS	CF: Unclear
				c. 11.4-14.6 yr (n=79)	c1.730 (1.800)		5. No 6. No	
				d. >14.6 yr (n=79)	d1.817 (1.936)			
<b>GRADE</b> assessmen	nt:							
Study design:	+4	1 prospective coh	ort study, 1 retrosp	ective cohort study				
<b>Study limitations:</b>	-1	Some limitations:	Selection bias high	in 2/2; Attrition bias low	in 2/2; Detection bias low in 2/2; un	clear in 2/2		
Consistency:	0				with older age at HSCT, one p-value			
<u>Directness:</u>	0	Results are direct,	population and out	comes broadly generaliz	able; PFT quality good (2/2 stated re	ference values and 2/	2 the use if ATS guidelir	ies)
Precision:	-1	Precision cannot b	oe judged as 1/2 sho	w results with p-value o	nly and 1/2 shows results with Hazar	d rate but without 959	%CI	
Publication bias:	0	Unlikely						
Effect size:	0	No large magnitud						
Dose-response:	0	No clear age respo	· ·					
Plausible confound		No plausible confo	ounding					
Quality of evidence		⊕⊖⊖ row						
Conclusion:					ncer survivors older vs. younger at all	ogeneic HSCT.		
				L non-significant effect [I				
Comment:	Onl	y univariable compa	rison between CCS	older vs. younger at allo	geneic HSCT and effect measure in o	ne 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	Ginsberg,	317 CCS	0 - >5 years	241 (76%)	Z-score Mean (SD) at last	P-value of ANOVA	1. No	Retrospective cohort
risk of restrictive	2010 (3)	(PFT post			post-transplant test		2. Yes	SB: High risk
abnormalities in		HSCT)			FVC	0.0263		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	a1.202 (1.234) b1.707 (1.410) c1.720 (1.668) d17.796 (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%)		P-value from Student paired t-test, >10yr vs. <10yr	1. Yes 2. Yes Polgar G, Rev Resp Dis, 1979	Retrospective cohort SB: High risk AB: Low risk DB: Low risk
				Age at HSCT >10yr vs. <10yr	Higher <b>TLC</b> when older at HSCT (no numbers stated)	0.08	3. No 4. No 5. No 6. No	CF: High risk
GRADE assessment: Study design: Study limitations: Consistency: Directness: Precision: Publication bias: Effect size: Dose-response: Plausible confoundir	+4 -2 0 -1 -1 0 0 0	No important inco Population and ou Precision cannot b Unlikely No large magnitud No clear age respo No plausible confo	Selection bias high possistency. No sign atcomes broadly goe judged as 2/2 sl de of effect pose relationship	nificant effect on TLC i	s low in 2/2; Detection bias lov in 2 studes and significant effe lity unsure (2/2 stated referen lue only	ect on FVC in 1 study		72
Quality of evidence: Conclusion:	_	→ → VERY LOW onsistent findings fo	r restrictive abnor	malities (TLC) in CAYA	A cancer survivors older vs. yo	unger at allogeneic HSCT		
		~		· · ·	[LC]; 356 participants)			
Comment:	On	ly univariable compa	rison between CC	S older vs. younger at	t allogeneic HSCT and no effec	t measure		

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	· · · · · · · · · · · · · · · · · · ·	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias	
1a What is the	e risk of <u>hyperinflatio</u>	on in younger com	pared to older age a	t HSCT?					
NI A d									

Publication bias:

0 Unlikely

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</u> capacity impairment younger compared to	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 <sub>corr</sub>	Hazard Ratio (p-value) Older age at HSCT continuously, per year	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999 3. No	Prospective cohort SB: High risk AB: Low risk DB: Low risk CF: Unclear
older age at treatment?					64% DLCO <sub>corr</sub> (<80%pred)	1.102 (0.005)	4. Yes: ATS 5. No 6. No	
	Ginsberg, 2010 (3)	317 CCS (PFT post HSCT) 133 CCS	0 - >5 years	241 (76%)	Z-score Mean (SD) for DLCO at last post- transplant test	P-value of ANOVA	1. No 2. Yes Rosenthal M, Thorax, 1993, Hankinson JL,	Retrospective cohort SB: High risk AB: Low risk DB: Low risk
		(PFT pre and post HSCT)		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)	a1.649 (1.830) b1.889 (1.531) c1.791 (1.665) d2.182 (1.341)	0.432	Am J Respir Crit Care Med, 1999 3. No 4. Yes: ATS 5. No 6. No	CF: Unclear
	Leung 2007 (5)	155 CCS	Median 9 (range 3.1-15.9)	155 (100%)		Hazard Ratio (95%CI) Older age at HSCT continuously, per year	1. No 2. No 3. No 4. No 5. No	Prospective cohort SB: Low risk AB: Low risk DB: Low risk CF: Low risk
					35% DLCO (<80%pred)	1.1 (1.04-1.17)	6. No	0 <u>2</u> 0
GRADE assessment Study design: Study limitations: Consistency:	:: +4 -1 0	Some limitations	: Selection bias high			ction bias low in 3/3; Con	founding unclear in 2	/3, low in 1/3
Directness:  Precision:	-1 -1	Population and o guidelines)	utcomes broadly ge	eneralizable; PFT qu	allty unsure (not homogeneou	us across studies, 2/3 stat	ed reference values a	

Effect size:

Dose-response:

Plausible confounding:

Quality of evidence:

Conclusion:

(3 studies; 2 significant effects, 1 non-significant effect; 561 participants)

Comment:

O No large magnitude of effect

No clear age response relationship

No plausible confounding

VERY LOW

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 obstructive 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	Anlyses: a. No vs limited cGvHD b. No vs extensive cGvHD c. No/Grade I vs Grade II-IV aGvHD	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 <b>Obstructive</b> 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 Study design: Study limitations: Consistency:	+4 1 -2 S 0 N	Some limitations: Se No important incon		2/2; Attrition bias lo	w in 2/2; Detection bias	s low in 2/2; Confounding malities with developmen	_	
<u>Directness:</u> <u>Precision:</u>	-1 I					ence values and 2/2 the uonfidence interval, 1/2 p		lged as results shown as

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:	$\oplus \ominus \ominus \ominus$ 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 restrictive abnormalities in patients with cGvHD compared to patients without cGvHD?	Madanat- Harjuoja, 2014 (6)	51 CSS with hematological disease	Chronic GvHD: - 55% No - 22% limited - 23% extensive  Acute GvHD: - 43% No/Grade I - 57% Grade II-IV	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	:	•		•				
Study design:	+4 1	retrospective coh	ort study					
Study limitations:	-1 Sc	ome limitations: Se	election bias high in	1/1; Attrition bias lo	ow in 1/1; Detection bia	as low in 1/1; Confoundir	g low in 1/1	
Consistency:		ne study only						
<u>Directness:</u>					y good (2/2 stated refe	rence values and 2/2 the	use if ATS guidelines)	
Precision:		•	only 1 study, no effe	ct size not shown				
Publication bias:		nlikely						
Effect size:		o large magnitude	of effect					
Dose-response:		ot applicable	din a					
<u>Plausible</u>	0 N	o plausible confou	inaing					
confounding:		VEDVLOW						
Quality of evidence Conclusion:		VERY LOW	hnormalities (EVC) :	n CAVA cancor surv	ivers after extensive ch	ranic GyUD and acuta Co	(UD Grado II IV vc. no (	CVUD
Conclusion:				ii CATA cancer Surv	ivors after extensive cn	ronic GvHD and acute Gv	nno Grade II-IV VS. NO C	טחענ.
Comments:		significant effect; only with some li						
Comments:	One study	only with some in	ilitations					

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	Leung 2007 (5)	155 CCS	Median 9	155 (100%)		Hazard Ratio (95%CI)	1. No	Prospective cohort		
risk of <u>diffusion</u>			(range 3.1-				2. No	SB: Low risk		
<u>capacity</u>			15.9)	cGvHD (26%)	34% DLCO (<80%pred)	1.96 (1.12-3.44)	3. No	AB: Low risk		
impairment in				No cGvHD (74%)			4. No	DB: Low risk		
patients with							5. No	CF: Low risk		
cGvHD compared							6. No			
to patients										
without cGvHD?										
GRADE assessment	-									
Study design:	+4	1 prospective coh	•							
Study limitations:	0		lection bias low in 1	/1; Attrition bias lov	v in 1/1; Detection bias low	in 1/1; Confounding low i	n 1/1			
Consistency:	NA	One study only								
<u>Directness:</u>	-1		· , ,	•	alues and no use of ATS gui	idelines stated)				
<u>Precision:</u>	-1	•	, only 1 study but p	ecise results with sr	mall confidence interval					
Publication bias:	0	Unlikely								
Effect size:	0	No large magnitud	de of effect							
<u>Dose-response:</u>	0	Not applicable								
Plausible confoundi	ing: 0	No plausible confo	ounding							
Quality of evidence		∋⊖ rom								
Conclusion:					cancer survivors with chror	nic GvHD vs. no cGvHD.				
	(1 stud	(1 study; 1 significant effect, 155 participants)								
Comments:	One st	tudy only with som	e limitations							

# 1c Infection during hematopoietic stem cell transplantation

1	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	n patients who had a	pulmonary infec	tion during HSCT compared	to patients withou	ut pulmonary infection during HSCT	?	
N	o 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	Leung 200 (5)	7 155 CCS	Median 9 (range 3.1- 15.9)	Allogeneic: 155 (100%)	Number of CCS with respective parameter below predicted values	Hazard Ratio (95%CI)	1. No 2. No 3. No 4. No	Prospective cohort SB: Low risk AB: Low risk DB: Low risk
with total body irradiation as				TBI: 123 (85%)	41 FEV1/FVC (<85%pred)	2.39 (1.10-5.74)	5. No 6. No	CF: Low risk
conditioning for HSCT?	Hoffmeister, 2006 (7)	,	Median 10.5 (range 5-27.5) No TBI: n=53	Allogeneic: 202 (94%) Analyses		Multivariate Analysis Odds Ratio (95%CI)	1. No 2. Yes: Rosenthal M, Thorax, 1993; Crapo RO, Am Rev Respir Dis, 1981;	Retrospective cross-sectional SB: High risk AB: Low risk
			FTBI: n=133 1.2Gy: n=37 >1.2Gy: n=96 SFTBI: n=29	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	a. 0.1 (0.0-1.4) b. 0.9 (0.3-2.8) c. 0.1 (0.0-0.5)	Crapo RO, Bulletin Europeen de Physiopathologie Respiratoire, 1982 3. No 4. Yes: ATS 5. No 6. No	DB: Low risk CF: High risk
GRADE assessment	:							
Study design:		•	hort study, 1 retros	•	•			
Study limitations:					Attrition bias low in 2/2; Dete			
Consistency:		non-TBI with no	significant associati	on.	nt reduction in FEV1/FVC in C			
<u>Directness:</u>		•		•	ality unsure (not homogeneo	us, 1/2 stated refere	nce values and 1/2 the	use if ATS guidelines)
Precision:			2/2 show precise re	sults with small cor	itidence interval.			
Publication bias:		0 Unlikely	of offort in one of	ıdı				
Effect size:		<ul><li>1 Large magnitude</li><li>0 Not applicable</li></ul>	e of effect in one stu	iuy				
<u>Dose-response:</u> <u>Plausible confoundi</u>	ng:	0 No plausible cor	nfounding					
Quality of evidence		⊕⊖⊖ VERY LOW	inounum <sub>6</sub>					
Conclusion:	1	nconsistent findings. I mentioned). No signifi	cant effect of differe	ent fractioning (one	* *			nly, fractioning not
Comments					ffect [different fractioning of	i Bij; 370 participants	)	
Comments:		Two studies with some	e ilinitations but higi	i 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 restrictive abnormalities for patients treated with total body irradiation as	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
conditioning for HSCT?	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 <b>restrictive</b> 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
Study design: Study limitations: Consistency: Directness: Precision: Publication bias: Effect size: Dose-response: Plausible confoundi	+4 -2 0 -1 -1 0 1 0 ng: 0	Some limitations No inconsistency Population and of Important impre Unlikely Large magnitude Not applicable No plausible con	s: Selection bias high y, both studies repoi putcomes broadly go- cision, both studies e of effect on one stu- founding	t reduction in TLC in ( eneralizable; PFT quali show precise results, udy	trition bias low in 2/2; Detect CAYA cancer survivors expose ty unsure (1/2 stated referen but the 95%CI but is large in o	d to TBI. ce values and 1/2 the one study	e use if ATS guideline:	5)
Conclusion:  Comments:	fract (2 st	ioning (one study). udies; 2 significant (		1 non-significant effe	urvivors after TBI as condition et [different fractioning of TB		BI. INO SIGNIFICANT EFF	ect of different

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 diffusion capacity impairment 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	:						•	
Study design:	+4	1 prospective of	cohort study					
Study limitations:	(	No limitations:	Selection bias low i	n 1/1; Attrition bias	low in 1/1; Detection bias I	low in 1/1; Confounding I	ow in 1/1	
Consistency:	N.A	A One study only	1					
<u>Directness:</u>	-1		-		(no reference values and n		nes stated)	
Precision:	-1		ion, only 1 study bu	t precise results wit	h small confidence interval			
Publication bias:	(	<i>'</i>						
Effect size:	1	L Large magnitud						
<u>Dose-response:</u>	(							
Plausible confoundi			onfounding					
Quality of evidence		⊕⊕ MODERATE		. (5. 66)				
Conclusion:					'A cancer survivors after TB	as conditioning for HSC1	vs. no TBI.	
0		,, ,	effect, 155 participa	nts)				
Comments:	One	study with high pr	ecision					

# 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 obstructive 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 Study design: Study limitations: Consistency: Directness: Precision:	+4 -2 NA -1 -1	Some limitation One study on Population an	ly id outcomes broadly	igh in 1/1; Attrition bia	is low in 1/1; Detection bias u ality unsure (no reference val 1 shows p-value only			
Publication bias: Effect size: Dose-response: Plausible confoundi Quality of evidence Conclusion:	: 000	Not applicable No plausible c  → VERY LOW	confounding	es (FEV1) in CAYA cano	er survivors after cyclophosp	hamide vs. no cyclophosi	ohamide	
Comments:	(1 stu	dy; 1 significant	effect; 70 participa	•	, , ,			

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 restrictive 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
GRADE assessment	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

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
<u>Directness:</u>	-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
Study design: Study limitations: Consistency: Directness: Precision: Publication bias: Effect size: Dose-response: Plausible confounding	+4 0 0 -1 -1 0 0	No limitations One study on Population ar Some impreci Unlikely	ly nd outcomes broadly ision, only 1 study bo nitude of effect e	generalizable; PFT qu	1/1; Detection bias low 1/1; of ality unsure (no reference value) with small confidence interval	ues and use of guidelines	s stated)	
Quality of evidence Conclusion:	No s	•	on diffusion capacit ficant effect; 193 pa	· · · · · · · · · · · · · · · · · · ·	n CAYA cancer survivors after	cyclophosphamide vs. no	o cyclophosphamide.	
Comments:	One	study only with	non-significant 95%	CI and no information	on PFT quality.			

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

2a What is the risk of obstructive 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; Hlbbert 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 assessmen Study design: Study limitations:	h <b>t:</b> +4 -3	1 prospective o	•	low in 1/1: Attrition hi	as high 1/1 ; Detection bias	unclear 1/1: Confound	ing high in 1/1	
Consistency:	-5	One study only		low iii 1/1, Attiitioii bi	as flight 1/1 , Detection bias	unclear 1/1, Comound	ing mgm m 1/1	
Directness:	-1	, ,		generalizable; PFT qu	ality unsure (10 different re	eferences stated und us	e of ATS guidelines)	
Precision:	-2			-	ect size mentioned, one stud			
Publication bias:	0	Publication bia	•					
Effect size:	0	No large magni						
Dose-response:	0		esponse relationsh	ıp				
Plausible confound		No plausible co	nrounding					
Quality of evidence Conclusion:		→ VERY LOW	a obstructive about	malities with increasi	ng doses of cyclophosphami	ido		
Conclusion:		dy; 260 participa		mandes with intreasi	ig doses of cyclophosphami	iue		
Comments:			<u> </u>	no effect size mentior	ned or n-value			
Comments.	Offic s	tudy office, utilival	iable allalysis, allu	no chect size inelitior	ica 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 restrictive	Nysom 1998 (11)	94 leukemia CCS	Median 10.6 (range 3.4-23.4)	43 (46%)		Regression coefficient (95%CI), p-value:	1. No 2. Yes Reference form own	Retrospective cohort SB: High risk
abnormalities in CAYA survivors				Cumulative dose of CYC as continuous variable	17% (15/89) with reduced or raised <b>TLC</b>	Simple regression -0.11 (-0.23 – 0.01), 0.07	laboratory by adjusting published reference values (Quanjer PH, Pediatr Pulmonol. 1995;	AB: Low risk DB: Unclear CF: High risk

treated with different doses of CYC?	Multiple regression: -0.14 (-0.250.02), 0.02  Bull Eur Ph Respir, 198 Pediatr Pul 1996) 3. No 4. Yes	njer PH, ysiopathol 33: Stam H,
	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	
<u>Directness:</u>	-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	
<u>Dose-response:</u>	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	e risk of pulmonary	dysfunction in CAY	A treated with meth	otrexate compared	I 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 <u>obstructive</u>	abnormalities in	CAYA survivors treat	ed with different do	ses of MTX?			

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 restrictive 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 <b>TLC</b>	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
Study design: Study limitations: Consistency: Directness: Precision: Publication bias: Effect size: Dose-response: Plausible confound Quality of evidence Conclusion:	### 1 retrospective cohort study    Severe limitations:							ure stated)
Conclusion:		• •		n whole study and or	nly 16 exposed to high-dos	se 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 th	e risk of <u>hyperinflat</u>	<u>ion</u> in CAYA surviv	ors treated with diff	erent doses of MTX	?			

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 impairmer	nt in CAYA survivors t	reated with differe	nt doses of MTX?				

### 3b Age at exposure

PICO	Study	No. of participants	Follow-up (median/mean, range)	Methotrexate	Pulmonary function Outcomes	Effect size	Risk of bias
			yr				
3b What is the ri	sk in younger compar	ed 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 o	f pulmonary dysfunct	ion in CAYA tre	ated with gemcitabine com	pared to CAYA not	treated with gemcitabine?		
No study							

# PICO 5: Bleomycin

PICO	Study	No. of participants	Follow-up (median/mea n, range) yr	Bleomycin exposure	Pulmonary function Outcomes	Effect size		Risk of bias
5 What is the risk of obstructive 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	Univariable logistic regression comparing bleomycin yes/no Odds Ratio (p-value)	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Wang X, Pediatr	Retrospective cohort SB: High Risk AB: High Risk DB: Low risk CF: High Risk
					29% (14/49) FEV1 <80% pred	0.07 (<0.01)	Pulmonol, 1993 3. No	
					20% (10/49) FEF25–5% <68% pred	0.18 (<0.05)	4. Yes: ATS 5. No 6. No	
					24% (12/49) Obstructive (FEV1/FVC <80%pred, FEV1<80%pred or FEF25-75<68%pred with normal TLC)	0.27 (NS)  More in non-exposed		
	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

		FEV1 <80% pred 50% (3/6) bleomycin 50% (7/15) no bleomycin	(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 co	hort study			
Study limitations:	<ul> <li>Severe limitations: Selection bias high in 2/1, lo</li> </ul>	w in 1/3; Attrition bias high in 1/3, le	ow 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	I risk for obstructive abnormalities in	n CAYA survivors exposed	to bleomycin.	
<u>Directness:</u>	0 Population and outcomes broadly generalizable				
Precision:	-1 Precision cannot be judged as 2/3 show p-value	e only and 1/3 shows OR but withou	t 95%CI. All studies perfor	med univariable analys	is 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, F	EF25-75, FEV1/FVC) after bleomycir	n vs. no bleomycin in CAY	A cancer survivors.	
	(3 studies; 2 significant effects, 1 non-significant effect	t; 213 participants)			
Comment:	All three studies with univariable analysis only and all	report results with p-values only an	d without confidence inte	rvals. Two studies with	less than 50
	participants.				

PICO	Study	No. of participants	Follow-up (median/mea n, 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	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,	Prospective cohort SB: Low risk AB: low risk DB: low risk CF: high risk
				TLC <75%pred and FEV1 >80%pred) 19% (8/42) bleomycin 27% (21/79) no bleomycin	(00 =00)	2005 5. No 6. Yes	
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	Univariable logistic regression comparing bleomycin yes/no Odds Ratio (p-value)	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999;	Retrospective cohort SB: High Risk AB: High Risk DB: Low risk
				24% (12/49) FVC <80% pred	0.15 (<0.05)	Wang X, Pediatr Pulmonol, 1993 3. No	CF: High Risk
				15% (7/49) TLC <77% pred	0.27 (NS)	4. Yes: ATS 5. No	
				15% (7/49) Restrictive disease (TLC <77%)	0.27 (NS)	6. No	
Denbo, 2014 (13)	21 Osteo- sarcoma survivor	Mean 20 yr (SD +/-9)	6 (28%)	Number of CCS with abnormal results per parameter	Univariate analysis comparing bleomycin yes/no (p-value)	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Miller A, Am Rev	Prospective cohort SB: low risk AB: low risk DB: unclear
				FVC <80%predicted 50% (3/6) bleomycin 36% (5/14) no bleomycin	0.642	Respir Dis, 1983 3. No 4. Yes: ATS, Morris AH, 1984	CF: high risk
				TLC <75%predicted 17% (1/6) bleomycin 33% (7/15) no bleomycin	0.623	5. No 6. No	
Mulder 2011 (9)	193 CCS	Median 17.9 (range 5.6- 36.8)	110 (57%)	Total 34/193 Restrictive	Comparison of bleomycin yes/no Odds Ratio (95%CI) 1.5 (0.38-5.97)	1. No 2. No 3. No 4. No	Retrospective cohort SB: Low risk AB: Low risk DB: Low risk
				(TLC or FVC <75%)	1.5 (0.50 5.57)	5. No 6. No	CF: Low risk

#### **GRADE** assessment:

Study limitations:

Study design: +4 3 retrospective cohort studies, 2 prospective cohort studies

-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.

<u>Directness:</u>	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
<u>Dose-response:</u>	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/mea n, 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	:		•				0.110	•
Study design: Study limitations: Consistency: Directness: Precision: Publication bias: Effect size: Dose-response:	+4 -3 0 0 -1 0 0	Severe limitat No inconsiste Population ar Precision can Publication bi	ncy. Both studies nd outcomes broa not be judged as ? ias unlikely nitude of effect	show that hype adly generalizable	ttrition bias high in 1/2, low in 1/2 rinflation is not associated with ble e; PFT quality good (both studies many with p-value only and 2/2 univaria	eomycin exposure. nention reference values a		

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/mea n, 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 Osteosarco ma 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 Osteosarco ma survivor	Mean 20 yr (SD +/-9)	6 (28%)	Number of CCS with abnormal results per parameter  DLCO <sub>corr</sub> <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

+4 2 retrospective cohort studies, 2 prospective cohort studies
-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
-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
-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)
-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
0 Publication bias unlikely
0 No large magnitude of effect
0 Not applicable
0 No plausible confounding
⊕⊖⊖ VERY LOW
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)
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.

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 obstructive 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	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 assessmen Study design: Study limitations: Consistency:	t: +4 -2 0		ons: Selection bias high in 1/1	.; Attrition bias lov	v in 1/1; Detection bias k	ow in 1/1; Confoundir	ng high in 1/1	

<u>Directness:</u>	Population and outcomes broadly generalizable; PFT quality good (reference values and lung function procedures mentioned)
Precision:	Precision cannot be judged as results are shown as p-value only, univariable analysis, only one study
Publication bias:	Publication bias unlikely
Effect size:	No large magnitude of effect
Dose-response:	No clear dose response relationship
Plausible confounding:	No plausible confounding
Quality of evidence:	⇒⇔ VERY LOW
Conclusion:	significant effect for obstructive abnormalities in CAYA cancer survivors exposed to higher doses (≥60IU/m²) of bleomycin vs. lower doses (<60IU/m²).
	study; 143 participants, 34 exposed to bleomycin)
Comments:	sults 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)	5 143 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:		•	ve cohort study	. h: 1 /1 . A.L	an bias law in 1/1. Datastic	a biaa law ia 1/1. Caafawa	din - bish in 1/1	
Study limitations:		<ol> <li>Severe limita</li> <li>One study on</li> </ol>		nign in 1/1; Attriti	on bias low in 1/1; Detection	n bias low in 1/1; Confoun	aing nign in 1/1	
Consistency: Directness:		•	•	v generalizable: DE	T quality good (reference va	lues and lung function are	ocaduras mantionad)	
Precision:		•		, •	p-value only, univariable and	•	cedures memoried)	
Publication bias:		0 Publication b	, 0	saits are snown as	p value offiy, affivariable and	21y313		
Effect size:			nitude of effect					
Dose-response:		0 0	response relations	hip				
Plausible confoundi	ng:	0 No plausible	•	•				
Quality of evidence		OO VERY LOW						
Conclusion:	Inci	eased risk for res	trictive abnormalitie	es (TLC) in CAYA ca	ncer survivors after higher d	oses (≥60IU/m²) of bleom	ycin vs. lower doses (	<60IU/m²) of
	ble	omycin in CAYA ca	ncer survivors.					
	(1 s	tudy; 143 particip	ants)					
Comments:	Res	ults reported from	n univariable analys	is and as p-values	only. Small sample size expo	sed to bleomycin in total.		

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

Effect size:  Dose-response:	0 0 0 ng: 0	No large magni	tude of effect esponse relationship					
Precision: Publication bias:	-1 0	Precision cannot Publication bias		s are shown as p-v	alue only, univariable analysis			
Study limitations: Consistency: Directness:	0	One study only			uality good (reference values			
GRADE assessment Study design:	+4 -2	1 retrospective	•	rh in 1/1. Attrition	bias low in 1/1; Detection bias	low in 1/1. Confoundin	a hiah in 1/1	
5a What is the risk of hyperinflation in CAYA survivors associated with different doses of bleomycin?	Record, 201 (1)	5 143 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

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 diffusion capacity impairment 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 20 (17)	21	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	•	ort studies, 1 retros	•	•			
Study limitations:		-2	Severe limitations unclear in 1/2	s: Selection bias high	n in 2/3, low in 1/2	; Attrition bias low in 3/3; Dete	ection bias low in 1/3, u	ınclear in 2/3; Confoui	nding high in 2/3,
Consistency:		0	No inconsistency.	All studies show no	significant associa	tion between cumulative dose	of bleomycin and diffu	usion capacity impairn	nent.
<u>Directness:</u>		-1	Population and or	utcomes broadly gei	neralizable; PFT qu	ality unsure (all studies mentic	on reference values, on	e mentions lung funct	ion procedures used)
Precision:		-1	Important impred	cision, 2/3 show sho	w p-value only, 1/3	3 report Odds Ratio and 95%CI,	, allreport univariable a	nalysis only	
Publication bias:		0	Publication bias u	•					
Effect size:		0	No large magnitu						
<u>Dose-response:</u>		0		ponse relationship					
Plausible confounding		0	No plausible conf	ounding					
Quality of evidence			O VERY LOW	1100					
Conclusion:			•	•	•	igher doses of bleomycin vs. lo	•	n in CAYA cancer survi	vors.
		•				ticipants exposed to bleomycir	•		
Comments:		All S	tudies report their	results as univariable	ie anaiysis only. Ho	mogeneous outcome and cuto	off definition across all	studies.	

# 5b Age at exposure

PICO	Study	No. of participants	Follow-up (median/mean, range) vr	Bleomycin exposure	Pulmonary function Outcomes	Effect size	Risk of bias	
5b What is the	he risk in younger compare							

#### No study

### PICO 6: Busulfan

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

6 What is the risk of <u>obstructive</u> abnormalities in CAYA treated with busulfan compared to CAYA not treated with 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>restrictive</u> abnormalities in CAYA treated	Armenian, 2015 (14)	121 CCS	Median 17.1 (6.3-40.1)	15 (12.4%)		Univariable logistic regression Odds Ratio (95%CI)	1. Yes 2. No 3. No 4. Yes: ATS,	Prospective cohort SB: Low risk AB: low risk
with busulfan compared to CAYA not treated with busulfan?					29 Restrictive (TLC<75% and FEV1≥80% predicted) 13% (3/15) busulfan 24% (26/106) no busulfan	0.8 (0.2-2.9)	Miller MR, Eur Respir J, 2005 5. No 6. Yes	DB: low risk CF: high risk
GRADE assessment	:							
Study design:	+4	Prospective co	hort study					
Study limitations:	-1	Some limitatio	ns: Selection bias low in 1/1;	Attrition bias low ir	n 1/1; Detection bias low in	n 1/1; Confounding high	n in 1/1	
Consistency:	0	One study only	<i>'</i>					
<u>Directness:</u>	-1	Population and	d outcomes broadly generalize	able; PFT quality ur	sure (no references ment	ioned, lung function pro	ocedure mentioned	
<u>Precision:</u>	-1	One study only	r, univariable comparison, res	ults shown as OR a	nd 95%CI			
<u>Publication bias:</u>	0	Unlikely						
Effect size:	0	No large magn						
<u>Dose-response:</u>	0	Not applicable						
<u>Plausible</u>	0	No plausible co	onfounding					
confounding:								
Quality of evidence	: 0000 v	VERY LOW						
Conclusion:	_		trictive abnormalities (TLC<75 15 participants exposed to bu	·	oredicted) after busulfan v	s. no busulfan in CAYA	cancer survivors.	
Conclusion:			on between CCS exposed to b		nall 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 com	pared to CAYA not t	reated with 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	Armenian,	121 CCS	Median 17.1	15 (12.4%)		Univariable logistic	1. Yes	Prospective cohort
of <u>diffusion</u>	2015 (13)		(6.3-40.1)			regression	2. No	SB: Low risk
<u>capacity</u>						Odds Ratio (95%CI)	3. No	AB: low risk
impairment in						0.1(0.1.1.0)	4. Yes: ATS, Miller	DB: low risk
CAYA treated					42 Diffusion impairment (DLCOcorr<75% predicted)	0.4 (0.1-1.6)	MR, Eur Respir J,	CF: high risk
with busulfan					13% (3/15) busulfan		2005	
compared to CAYA not treated					37% (39/106) no		5. No 6. Yes	
with busulfan?					busulfan		0. 163	
GRADE assessment	:							
Study design:	+4	Prospective co	hort study					
Study limitations:	-1	Some limitatio	ns: Selection bias lo	w in 1/1; Attrition bia	as low in 1/1; Detection bias	low in 1/1; Confounding	g high in 1/1	
Consistency:	0	One study only	1					
<u>Directness:</u>	-1	Population and	d outcome broadly ខ្	generalizable; PFT qu	ality unsure (no references r	mentioned, lung functior	n procedure mentione	d)
Precision:	-1	•	, univariable compa	rison, results shown	as OR and 95%CI			
Publication bias:	0	Unlikely						
Effect size:	0	0 0	itude of effect					
<u>Dose-response:</u>	0	Not applicable						
Plausible confoundi		No plausible co						
Quality of evidence	• •	⊖⊖ VERY LOW						
Conclusion:		_			after busulfan vs. no busulfa	an in CAYA cancer surviv	ors.	
				s exposed to busulfar				
Conclusion:	Only	univariable com	parison between CC	S exposed to busulfa	in and not exposed			

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

### 6b Age at exposure

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

No study

### PICO 7: Nitrosureas

PICO	Study	No. of participants	Follow-up (median/mean,	Nitrosurea exposure	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
			range) yr					
7 What is the risk o	of <u>obstructive</u>	abnormalities in CA	YA treated with nitr	osureas compar	ed 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 restrictive 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	t:							
Study design:	+4	1 prospective col	nort study					
Study limitations:	-1	Some limitations	: Selection bias low i	n 1/1; Attrition b	ias low in 1/1; Detection bias	low in 1/1; Confounding	high in 1/1	
Consistency:	0	, - ,						
<u>Directness:</u>	-1	· · · · · · · · · · · · · · · · · · ·		· ·	juality unsure (no reference m	nentioned, lung function	procedure mentione	d)
<u>Precision:</u>	-1	, ,,	inivariable analysis,	results shown as	OR with 95%CI			
Publication bias:	0							
Effect size:	0		de of effect					
<u>Dose-response:</u>	. 0		. ,					
Plausible confound		No plausible conf	ounding					
Quality of evidence		⊖⊖⊖ Very low		-liting /TLC and F	-\/1\ -ft:t	:huaaaa in CAVA aanaa		
Conclusion:			nts; 12 exposed to n		EV1) after nitrosureas vs. no n	iiti Osureas III CATA Cance	er Survivors.	
Comment:			omparison, small sar		d to nitrosuross			
Comment.	UI	ny one univariable c	ompanson, small sal	Tiple Size exposed	a to mitrosureas			

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 o	f <u>hyperinflation</u>	in CAYA treated v	with nitrosureas co	mpared to CAYA n	ot treated with nitrosureas?	<b>?</b>		
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 diffusion capacity impairment in CAYA treated	Armenian, 2015 (13)	121 CAYA	Median 17.1 yrs (6.3-40.1 yrs)	9.9%	Total 42 diffusion	Univariable logistic regression Odds Ratio (95%CI)	1. Yes 2. No 3. No 4. Yes: ATS 5. No	Prospective cohort SB: Low risk AB: low risk DB: low risk CF: high risk
with nitrosureas compared to CAYA not treated with nitrosureas?					abnormality (DLCO<75% predicted) 42% (5/12) nitrosureas 34% (37/109) no nitrosureas		6. Yes	
GRADE assessment	<b>:</b>							
Study design:	+4	1 prospective c	ohort study					
Study limitations:	-1	Some limitation	ns: Selection bias lo	w in 1/1; Attrition I	bias low in 1/1; Detection bia	as low in 1/1; Confoundir	ng high in 1/1	
Consistency:	0	One study only						
<u>Directness:</u>	-1	•	•	<del>-</del>	quality unsure (no reference	e mentioned, lung function	on procedure mentio	ned)
Precision:	-1		, univariable analys	is, results shown as	S OR with 95%CI			
Publication bias:	0	Unlikely						
Effect size:	0	No large magni	tude of effect					
<u>Dose-response:</u> Plausible confoundi		Not applicable No plausible co	nfounding					
Quality of evidence		No plausible co	mounding					
Conclusion:			diffusion canacity	imnairment (DLCO	) after nitrosureas vs. no nitr	osureas in CAVA cancer s	survivors	
55.1614010111			nts; 12 exposed to r	•	, 4.10	ou. cao in ortir cancer		
Comment:			omparison, small sa	· · · · · · · · · · · · · · · · · · ·	to nitrosureas			

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

No study

### 7b Age at exposure

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

### 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	Oguz 2007 (18)	75 Lymphoma survivors	Median 5 (2-13)	Group 1: Chemo and Radio (n=23)	Mean (±SD) of selected % predicted values	Comparison Group I vs Group II (student t-test)	1. No 2. Yes: References recommended by European Coal and	Retrospective cross- sectional SB unclear AB: low risk
with radiotherapy exposing lung tissue compared				Group 2: Chemo only (n=52)	FEV1 Group 1: 95.43 (± 16.47) Group 2: 105.09 (± 19.01) FEV1/FVC	p=0.038	Steel Community; Severity acc. to ATS pulmonary function laboratory guidelines	DB: unclear CF: unclear
to CAYA not treated with radiotherapy exposing lung					Group 1: 96.43 (± 9.15) Group 2: 99.88 (± 11.93)	p=0.221	3. No 4. No 5. No 6. No	
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	Multivariable analysis, CSI (yes/no) leads to reduction in FEV1:	1. Yes 2. No 3. No 4. No	Prospective cross- sectional SB: high risk AB: low risk
					36/69 FEV1 <85% predicted 23/69 FEV1 <80% predicted	p<0.001	5. No 6. No	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%)	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	Retrospective cohort SB: high risk AB: low risk DB: low risk CF: high risk
					25% (24/97)radiotherapy 28% (13/46) no radiotherapy		5. No 6. Yes	
	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	OR, 95%CI	1. No 2. Yes 3. No 4. Yes (ATS)	Prospective cohort SB: high risk AB: low risk DB: low risk
					<b>FEV1</b> (FEV1 <80% pred) RT yes: 71.4% abnormal RT no: 34.2% abnormal	4.29 (1.35 – 13.58), p=0.005	5. No 6. No	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 5. Yes CF: low risk  Effect of radiotherapy vs. no Coefficient -1.306 6. No  radiotherapy on 95%CI -2.055  longitudinal changes in 0.558 p=0.001  FEV1 (intercept)
	MMEF  Effect of radiotherapy vs. no Coefficient -0.664  radiotherapy on 95%CI -1.583 —  longitudinal changes in 0.253 p=0.156  MMEF (intercept)
GRADE assessment: Study design: Study limitations: Consistency:	<ul> <li>2 retrospective cohort study, 1 retrospective cross-sectional study, 1 prospective cross-sectional study, 1 prospective cohort study</li> <li>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</li> <li>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</li> </ul>
Directness: Precision: Publication bias: Effect size: Dose-response: Plausible confounding:	Population and outcomes broadly generalizable, PFT quality unsure (reference mentioned in 5/5, lung function procedure mentioned in 0/5)  Important imprecision, 3/5 report p-values only, 2/5 report 95%CI, 1/5 performed univariable regression analysis, 2/5 performed multivariable analysis  Unlikely  No large magnitude of effect  Not applicable  No plausible confounding
Quality of evidence: Conclusion:	⊕⊖⊖ Very low 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	Jenney 1995	70 Leukemia	Median 4.2	14% (CSI, n=10)	Number of CCS with	Multivariable	1. Yes	Prospective cross-
tissue?	(8)	survivors	(0.6-18.5)	20% (TBI, n=14)	respective parameter below	analysis, CSI leads	2. No	sectional
					predicted values	to reduction in	3. No	SB: high risk
						FVC and TLC:	4. No	AB: low risk
					32/69 FVC <85% predicted	p<0.001	5. No	DB: unclear
					26/69 TLC <85% predicted		6. No	CF: unclear
					20/69 FVC <80% predicted			
					20/69 TLC <80% predicted			
	Record 2016	143 CCS	Mean 14.1 ±4.8	67.8%		Univariable	1. No	Retrospective cohort
	(1)		yrs	(n=97)		comparison Chi2	2. Yes	SB: high risk
						radiation yes/no	Wang X, Pediatr Pulmonol 2005;	AB: low risk DB: low risk
					Restrictive	p=0.33	Hankinson JL, Am J	CF: high risk
					(TLC<80% predicted)	ρ-0.33	Respir Crit Care Med 1999	Ci . High risk
					11% (11/97) radiotherapy		3. No	
					17% (8/46) no radiotherapy		4. Yes	
					. (=, =, = =============================		5. No	
							6. Yes	
	Mulder 2011	193 CCS	Median 17.9	40.9%		Odds Ratio	1. No	Retrospective cohort
	(9)		(5.6-36.8)	(n=79)		(95%CI) for	2. No	SB: low risk
	, ,		,	, ,		radiotherapy	3. No	AB: low risk
						yes/no	4. No	DB: unclear
					Total 28 restrictive	12.87 (3.37-49.08)	5. No	CF: low risk
					(TLC OR FVC <75%)	12.07 (3.37 13.00)	6. No	C1 . 10 W 115K
					Of those Exposed: 35%		0.110	
	Stone 2020	62 high-risk	Median 5.29	34%	FVC	OR, 95%CI	1. No	Prospective cohort
	(19)	neuroblastoma	(0.24-15.24)	(n=21)	(FVC <80% pred)	4.40 (1.34 - 14.51)	2. Yes	SB: high risk
					RT yes: 76.2% abnormal	p=0.010	3. No	AB: low risk
					RT no: 41.7% abnormal		4. Yes (ATS)	DB: low risk
							5. No	CF: high risk
					TLC	4.33 (1.39 –	6. No	· ·
					(TLC <80% pred)	13.50), p=0.005		
					RT yes: 66.7% abnormal	,,,,		
					RT no: 35.4% abnormal			
	Otth 2021	72 CCS	Median 9.4	70%		mixed effects	1. Yes	Retrospective cohort
	(20)	exposed to	(6.1 - 12.3)	(n=52)		multivariable	2. Yes	SB: high risk
		HSCT				linear	3. No	AB: low risk
						regression analysis	4. No	DB: low risk
					FVC		5. Yes	CF: low risk
					Effect of radiotherapy vs. no	Coefficient -1.473	6. No	
					radiotherapy on	95%CI -2.207 -		
					longitudinal changes in FVC	-0.739		
					-	p=<0.001		
					TLC			

	Effect of radiotherapy vs. no Coefficient -0.717							
	radiotherapy on 95%CI -2.051 –							
	longitudinal changes in TLC 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:	O 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.							
<u>Directness:</u>	-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							
<u>Dose-response:</u>	0 Not applicable							
Plausible confounding:	0 No plausible confounding							
Quality of evidence:	$\oplus \ominus \ominus \ominus$ 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	Oguz 2007 (17)	75 Lymphoma survivors	Median 5 (2-13)	Group 1: Chemo and Radio (n=23) Group 2:	Mean (±SD) of selected % predicted values	Comparison Group I vs Group II (student t-test)	oup I vs Group II  udent t-test)  2. Yes: references recommended by European Coal and Steel Community; Severity act. to ATS pulmonary function laboratory guidelines	Retrospective cross- sectional SB unclear AB: low risk DB: unclear CF: unclear
				Chemo only (n=52)	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)	p=0.043		
tissue?	Record 2016 (1)	143 CCS	Mean 14.1 ±4.8	67.8% (n=97)		Univariable comparison Chi2 radiation yes/no	1. No 2. Yes: Wang X, Pediatr Pulmonol 2005; Hankinson JL, Am J Respir Crit Care Med	Retrospective cohort SB: high risk AB: low risk DB: low risk
					hyperinflation (RV >120%pred or RV/TLC >28% pred) 46% (45/97) radiotherapy 30% (14/46) no radiotherapy	p=0.07	1999 3. No 4. Yes 5. No 6. Yes	CF: high risk

	Otth 202 (20)	21	72 CCS exposed to HSCT	Median 9.4 (6.1 – 12.3)	70% (n=52)	<b>RV</b> 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	•		•	-sectional study, 1 retrospective			
Study limitations:		-2	Some limitation low in 1/3, und		igh in 2/3, unclear	in 1/3; Attrition bias low in 3/3; I	Detection bias low in 2	2/3, unclear in 1/3; Co	onfounding high in 1/3,
Consistency:		0		tency between stud ciation between ex		now an association between hypedinal changes.	erinflation and radioth	nerapy exposing the Iu	ung tissue. One study
<u>Directness:</u>		-1	Population and	d outcomes broadly	generalizable, PF7	quality unsure (reference menti	ioned in 3/3, lung fund	ction procedure ment	ioned in 1/3)
Precision:		-1	Important imp	recision, precision of	cannot be judged a	is 2/2 report p-values only and 2,	/2 performed unviable	analysis only	
Publication bias:		0	Unlikely						
Effect size:		0	No large magn	itude of effect					
Dose-response:		0	Not applicable	!					
Plausible confoundir	ng:	0	No plausible co	onfounding					
Quality of evidence	:	<b>Ф</b> ӨС	⊖ Very low						
Conclusion:		Increas	sed risk for hypei	rinflation (RV, RV/TI	C) after radiother	apy exposing the lung tissue vs. r	no radiotherapy in CAY	'A cancer survivors in	2 studies and a trend in
		one stu	ıdy						
		(3 stud	ies; 292participa	nts; 172participant	s with radiotherap	y exposing the lung tissue)			
Comment:		2/3 stu		values only with a t	rend is towards m	ore hyperinflation in exposed CA	YA cancer survivors. O	utcome definition dif	fers between the

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	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
radiotherapy 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	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)	<b>DLCO</b> 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
iRADE assessment tudy design: tudy limitations:	+4 -2	Some limitations: in 2/6, unclear in	Selection bias hig 4/6	h in 4/6, low in 1,	ectional studies, 1 prospective cross /4, unclear in 1/4; Attrition bias low	in 6/6; Detection bias	low in 3/6, unclear in	n 3/6; Confounding low
Consistency:	0	No important inco	misistericy, iviost s	studies snow aittu	ision capacity impairment in CAYA o	ancer survivors expos	eu to radiotherapy ex	chosing inne tissue

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:	$\oplus \ominus \ominus \ominus$ 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/me an, range) yr	Radiotherapy exposing lung tissue	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
8a What is the risk for obstructive abnormalities associated with different doses and volumes of radiotherapy?	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	No correlation between severity of abnormal FEV1 z-score and total radiation dose: - r²=0.002 (very weak)  No correlation between severity of abnormal	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
- dose-volume relationship - impact of dose per fraction					- FEV1 z-score	FEV1 z-score and total radiation dose after taking body length into account: - r²=0.002 (very weak)		
	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	Multivariable log- binomial regression: Outcome: V10 (per 10% increase) Relative Risk (95%CI, p- value)	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,	Prospective cohort SB: High risk AB: Low risk DB: Unclear CF: Low risk
					51% FEV1 <80% pred 49% FEV1 <lln< td=""><td>1.07 (1.04–1.09, &lt;0.001) 1.06 (1.04-1.09, &lt;0.001)</td><td>accessed 2015; Quanjer PH, Eur Respir J, 2012 3. Yes 4. Yes: ATS 5. No 6. No</td><td></td></lln<>	1.07 (1.04–1.09, <0.001) 1.06 (1.04-1.09, <0.001)	accessed 2015; Quanjer PH, Eur Respir J, 2012 3. Yes 4. Yes: ATS 5. No 6. No	

	De 2015 (12)	49	Median 2.91	100%	Proportion of CCS with	Logistic regression with	1. No	Retrospective cohort
	DC 2013 (12)	Osteo	(range 0.01-	(n=49)	abnormal results per	radiation dose in Gy	2. Yes	SB: High Risk
		sarcoma	8.28)	()	lung function parameter	(cont.) and normal/ abnormal parameter Odds Ratio (p-value)	Hankinson JL, Am J Respir Crit Care Med, 1999; Wang X, Pediatr Pulmonol, 1993 3. No	AB: High Risk DB: Low risk CF: High Risk
					FEV1 <80% pred: 29%	Mean dose: 1.20; 0.01	4. Yes: ATS	
					(14/49)	Max dose: 1.12; <0.01	5. No	
					FFF2F 7F9/ -C09/ -		6. No	
					FEF25–75% <68% pred:	Mean dose: 1.18; <0.01		
					20% (10/49)	Max dose: 1.06; <0.05		
					Obstructive disease	Mean dose: 0.99; NS		
					(FEV1/FVC <80%, FEV1<80% or FEF25-75<68% with normal TLC): 24% (12/49)	Max dose: 1.03; NS Prescribed dose: 1.05; NS		
GRADE assessmen	t:				, , ,			
Study design:	+4	2 retrospective	cohort studies, 1 p	prospective cohort st	tudy			
Study limitations:	-3	Some limitation	s: Selection bias h	igh in 3/3; Attrition I	bias high in 2/3, low in 1/3; [	Detection bias low in 2/3, unc	lear in 1/2; Confounding	g high in 2/3
Consistency:	0		· ,			es below predicted or LLN wit	•	
<u>Directness:</u>	-1					od (in 3/3 reference values ar		
Precision:	-1		ecision 1/3 show p	precise results with s	mall confidence interval; 1/3	3 shows correlation coefficier	t only; 1/3 shows effect	size but without 95%CI
Publication bias:	0	Unlikely						
Effect size:	0	No large magni						
<u>Dose-response:</u>	+1	Dose-response	relationship					

Quality of evidence: ⊕⊖⊖⊖ Very low

Plausible confounding:

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

0 No evidence of possible confounding

PICO	Study	No. of participants	Follow-up (median/me an, 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: - r²=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 er fraction					- TLC z-score (n=23)	taking body length into account: - r <sup>2</sup> =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	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. 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	Prospective cohort SB: high risk AB: low risk DB: unclear CF: high risk
					31.2% TLC <75% pred	1.07 (1.01–1.13, 0.019)	3. Yes 4. Yes: ATS 5. No 6. No	
	Armenian, 2015 (14)	121 CAYA	Median 17.1 yrs (6.3-40.1)	73.6% (n=89)		Multivariable logistic regression Odds Ratio (95%CI)	1. Yes 2. No 3. No 4. Yes: ATS	Prospective cohort SB: Low risk AB: low risk DB: low risk
				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	1 ≤20Gy 1.6 (0.5-5.7) >20Gy 5.6 (1.5-2.1)	5. No 6. Yes	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		No     Yes: 10 different references for standardization	Prospective cohort SB: low risk AB: high risk DB: unclear
					TLC < 75%: 11%  Unclear how many received proton and photon beam, but of initially 303 eligible patients only 20 had proton beam	Larger <b>TLC% predicted</b> : photon beam CSI (p=0.002)	3. No 4. Yes: ATS 5. No 6. No	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	Logistic regression analysis with radiation dose in Gy (cont.) and normal/ abnormal parameter Odds Ratio (p-value)	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Wang X, Pediatr Pulmonol, 1993 3. No 4. Yes: ATS	Retrospective cohort SB: High Risk AB: High Risk DB: Low risk CF: High Risk
					FVC <80% pred: 24% (12/49)	Mean dose: 1.22; <0.01 Max dose: 1.10; <0.01	5. No 6. No	
					TLC <77% pred: 15% (7/49)	Mean dose: 1.30; <0.01 Max dose: 1.07; <0.05		

	The odds of developing restrictive abnormalities
	increased with increasing
	V dose beginning at V10
	Restrictive (TLC <77%) Mean dose: 1.30; <0.01
	15% (7/49) 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
<u>Birectiless.</u>	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
<u> </u>	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:	ncreased 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/me an, range) yr	Radiotherapy exposing lung tissue	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
8a What is the risk for hyperinflation associated with different doses and volumes of	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	Logistic regression with radiation dose in Gy (cont.) and normal/ abnormal parameter Odds Ratio (p-value)	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Wang X, Pediatr Pulmonol, 1993	Retrospective cohort SB: High Risk AB: High Risk DB: Low risk CF: High Risk
radiotherapy?					RV/TLC: >123% pred: 20% (10/49)	Mean dose: 1.30; <0.01 Max dose: 1.26; <0.05	3. No 4. Yes: ATS 5. No	
relationship - impact of dose per fraction						The odds of developing hyperinflation increased with increasing V dose beginning at V20	6. No	
					Hyperinflation	Mean dose: 1.29; <0.01 Max dose: 1.26; <0.01		

(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

<u>Directness:</u> 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

<u>Publication bias:</u> 0 Unlikely

Effect size:0No large magnitude of effectDose-response:+1Dose response relationshipPlausible confounding:0No plausible confounding

Quality of evidence:

 $\oplus\ominus\ominus\ominus$  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/me an, 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	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)	No correlation between severity of abnormal FEV1, TCL, and DLCO (z-score) and total radiation dose: - r²=0.13 (very weak)  No correlation between severity of abnormal DLCO (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					- DLCO z-score (n=21)	taking body length into account: - r <sup>2</sup> =0.03 (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  44.6% DLCO <sub>corr</sub> <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	Logistic regression analysis with radiation dose in Gy (cont.) and normal/ abnormal parameter Odds Ratio (p-value)	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Wang X, Pediatr Pulmonol, 1993 3. No 4. Yes: ATS	Retrospective cohort SB: High Risk AB: High Risk DB: Low risk CF: High Risk
				DLCO <sub>adj</sub> <65% pred: 9% (4/49) DLCO <65%pred: 14% (6/49)	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	5. No 6. No	

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
<u>Consistency:</u>	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
<u>Directness:</u>	-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)
<u>Precision:</u>	-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 correlation 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:	$\oplus \ominus \ominus \ominus$ 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	Pulmonary function Outcomes	Effect size	Risk of bias
8b What is the risk	in different radiother	apeutic fields? -	No study			

# 8c Age at exposure

PICO	Study	No. of participants	Follow-up (median/mea n, range) yr	Radiotherapy exposing lung tissue	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
8c What is the risk for obstructive 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 <sup>2</sup> <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)	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)	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)  <5 years >5 or <13 years	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)		

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.
<u>Directness:</u>	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%Cl 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:	$\oplus \ominus \ominus \ominus$ 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/mea n, 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 <sup>2</sup> =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. 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

	Multivariable logistic regression, adjusted for <5 years time since treatment >5 or <13 years OR (95%CI) >13 years: 1.0 (ref) 2.22 (0.15-33.44) (NS) 2.06 (0.45-9.51) (NS)
	Multivariable logistic regression, adjusted for time since treatment and <5 years bleomycin exposure >5 or <13 years OR (95%CI) >13 years: 1.0 (ref) 1.26 (0.06-25.63) (NS)
GRADE assessment:	1.30 (0.19-8.72) (NS)
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:	O 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%Cl and p-value not significant, 1/3 studies shows 95%Cl 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:	$\oplus \ominus \ominus \ominus$ 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/mea n, 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	Retrospective cohort SB: High Risk AB: High Risk DB: Low risk CF: High Risk
GRADE assessmen	t:						5. No 6. No	

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 0 Results and outcomes broadly generalizable. PFT quality is good (reference values and guidelines stated). Directness: 0 Imprecision 1/1 reports OR without 95%CI and p-value is not significant Precision: Publication bias: 0 Unlikely Effect size: 0 No large magnitude of effect 0 No clear relation with increase in the outcome with older age at time of radiotherapy Dose-response: 0 No evidence of possible confounding Plausible 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/mea n, 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 <sup>2</sup> =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 3.09(0.71-13.45)
	>13 years: 1.0 (ref)
	Multivariable logistic
	regression, adjusted for
	time since treatment
	and bleomycin exposure
	OR (95%CI)
	<5 years 3.64 (0.18-72.86)
	>5 or <13 years 2.74 (0.46-16.18)
	>13 years: 1.0 (ref)
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.
<u>Directness:</u>	0 Results broadly generalizable for CCS treated with radiotherapy exposing lung tissue. PFT quality is good (2/2 report reference values and guidelines used)
<u>Precision:</u>	-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:	B⊖⊖⊖ Very low
Conclusion:	lo 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	nportant 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 pulmonal combined with radiotherapy in			<b>.</b>		, , ,		• • •

# 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 obstructive 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	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
<b></b>	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)	Logistic regression analysis with surgery yes/no Odds Ratio (p-value) 8.0 (<0.01) 2.35 (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
					Obstructive (FEV1/FVC <80%, FEV1<80% or FEF25-75<68% with normal TLC): 24% (12/49)	5.89 (<0.05)		
	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 neuroblasto ma	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
<u>Directness:</u>	O Population and outcomes are generalizable. PFT quality is good (4/4 state references and guidelines used).
<u>Precision:</u>	-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
<u>Dose-response:</u>	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:	$\oplus \ominus \ominus \ominus$ 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%	Logistic regression with surgery yes/no Odds Ratio (p-value) 3.2 (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)	Fishers exact test p-value  0.347	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Miller A, Am Rev Respir Dis, 1983 3. No	Prospective cohort SB: low risk AB: low risk DB: unclear CF: high risk
					TLC <75% pred 1 Thoracotomy (2/15) vs ≥2 Thoracotomies (4/6)	0.031	4. Yes: ATS, Morris AH, 1984 5. No 6. No	
	Mulder 2011	193 CCS	Median 17.9	16.6%		Odds Ratio (95%CI)	1. No	Retrospective cohort
	(9)		(5.6-36.8)	(n=32)	34/193 Restrictive (TLC OR FVC <75%) Of those Exposed: 7.7%	for surgery yes/no 3.79 (1.25-11.50)	2. No 3. No 4. No 5. No 6. No	SB: low risk AB: low risk DB: unclear CF: low risk
	Stone 2020 (19)	62 high-risk neuroblasto ma	Median 5.29 (0.24-15.24)	23% (n=14)	FVC (FVC <80% pred) Surgery yes: 92.9% abnormal Surgery no: 41.5% abnormal	OR, 95%CI 18.20 (2.20 – 150.58), 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
					TLC (TLC <80% pred) Surgery yes: 64.3% abnormal Surgery no: 35.4% abnormal	3.28 (0.95 – 11.38), p=0.054		
GRADE assessment	:							
Study design: Study limitations:	-		ons: Selection bias	2 prospective cohort high in 3/5, low in 2	study 1/5; Attrition bias high in 1/5, lo	ow in 4/5; Detection bias	low in 3/5, unclear	in 2/5; Confounding
Consistency:		0 Most studies			A cancer survivors without tho	racic surgery have more	restrictive abnorma	lities, in remaining 3
<u>Directness:</u> <u>Precision:</u>		1 Results are ge 1 Important imp	neralizable. PFT q precision; 1/5 sho	uality is unsure (4/5	state references and guideline R and 95%CI, 1/5 shows OR bu		Odds Ratio but large	e 95%CI, in 2/5
Publication bias: Effect size: Dose-response:		One studies sl			abnormalities after ≥2 thoraco	otomies compared to on	e, but very small san	nple size.
Plausible confounding Quality of evidence		0 No evidence o ⊖⊖⊖ Very low	of possible confou	nding				
Conclusion:	Incr	eased risk for rest		ies (FVC, TLC, restric	tive) in CAYA cancer survivors	after thoracic surgery vs.	. CAYA cancer surviv	ors without thoracic

	(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 hyperinflation 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	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%	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	Retrospective cohort SB: High Risk AB: High Risk DB: Low risk CF: High Risk
					(10/49)	6.5 (<0.01)	4. Yes: ATS 5. No 6. No	
GRADE assessment Study design: Study limitations: Consistency: Directness: Precision: Publication bias: Effect size: Dose-response: Plausible confoundi	+4 -3 0 0 -1 0 0 0 0	Important lim Studies show Results are ge Important im Unlikely No large mag Not applicable No evidence of	generally more hypeneralizable. PFT que precision; 1/2 reporentude of effect	erinflation in ex ality is good (2/: ts odds ration w	Attrition bias high in 1/2, low in 1/posed CAYA cancer survivors, som 2 state references and guidelines uithout confidence interval, in 1/2	e are significant some n ised).	ot	
Quality of evidence Conclusion:	Incon	~			AYA cancer survivors after thoracions participants; 33 participants; 33 participants	· ·		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>diffusion</u> <u>capacity</u> <u>impairment</u> in CAYA treated with thoracic	De 2015 (12)	49 Osteo- sarcoma	Median 2.91 (range 0.01- 8.28)	18% (n=9)	Proportion of CCS with abnormal DLCO	Logistic regression with surgery yes/no Odds Ratio (p- value)	1. No 2. Yes Hankinson JL, Am J Respir Crit Care Med, 1999; Wang X, Pediatr Pulmonol, 1993	Retrospective cohort SB: High Risk AB: High Risk DB: Low risk CF: High Risk
urgery ompared to					DLCO <sub>adj</sub> <65% pred: 9% (4/49) Diffusion defect (DLCO <65%): 14% (6/49)	4. Yes: Al	3. No 4. Yes: ATS	
CAYA not treated with thoracic surgery?						1.07 (NS)	5. No 6. No	
<i>,</i>	Denbo, 2014 (13)	21 Osteo- sarcoma	Mean 20 yr (SD ±9)	N=15 with 1 thoracotomy	Proportion of CCS with abnormal DLCO	Fishers exact test p-value	1. No 2. Yes Hankinson JL, Am J	Prospective cohort SB: low risk AB: low risk
		Salconia		N=6 with ≥2 thoracotomies	DLCO <sub>corr</sub> < 75% pred 1 Thoracotomy (7/15) vs ≥2 Thoracotomies (2/4)	1.00	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
	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 neuroblasto ma	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 Study design: Study limitations:	+4 -2	Some limitation			study 2/4; Attrition bias high in 1/4, lov	w in 3/4; Detection bias		in 2/4; Confounding
Consistency: Directness: Precision:	0 -1 -1	Results are ge Important im	show similar results neralizable. PFT qu	ality is unsure (3/4 es show effect size	state references and guidelines with CI, 1/4 shows effect size (C s only		4 precision cannot l	pe judged as result is

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:	$\oplus \ominus \ominus \ominus$ 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)	Thoracic Surgery	Pulmonary function Outcomes	Effect size	Risk of bias
			yr				
9a What is the risk a	associated with differ	ent resection v	olumes?				

### No study

### 9b Age at exposure

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

No study

#### PICO 10: Combinations

PICO

#### 10a Thoracic surgery plus chemotherapy

Study

No. of

Follow-up

participants (median/mean,

0 OR not estimable, one study only

No large magnitude of effect

0 No evidence of possible confounding

0 Unlikely

⊕⊖⊖ Very low

Not applicable

		range) yr	chemotherapy				
of <u>obstructive</u> al	bnormalities aft	ter thoracic surgery	combined with pulr	notoxic chemotherapy (blec	omycin, CCNU, BCNU, Busu	ılfan, Cyclophos	phamide, Methotrexate
Study	No. of participants	Follow-up (median/mean, range) yr	Thoracic surgery and chemotherapy	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
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
+4 -1 0	Some limitation	ons: Selection bias l ly		• •		ling, low in 1/1	
	Study  Mulder 2011 (9)  +4 -1	Study No. of participants  Mulder 2011 193 CCS (9)  +4 1 retrospective -1 Some limitation one study on	Study  No. of Follow-up participants (median/mean, range) yr  Mulder 2011 193 CCS Median 17.9 (5.6-36.8)  +4 1 retrospective cohort study -1 Some limitations: Selection bias 0 One study only	Study  No. of Follow-up Thoracic surgery and range) yr chemotherapy  Mulder 2011 193 CCS Median 17.9 Bleomycin plus surgery 1.6% (n=3)  Bleomycin only 50.8% (n=98)  Hand I retrospective cohort study Some limitations: Selection bias low in 1/1; Attrition to 0 One study only	Study  No. of Follow-up Thoracic surgery Pulmonary function Outcomes  range) yr chemotherapy  Mulder 2011 193 CCS Median 17.9 Bleomycin plus (9) (5.6-36.8) surgery 1.6% Restrictive impairment (n=3) (TILC OR FVC <75%) Bleomycin only vs Bleomycin only 50.8% (n=98)  Hand Thoracic surgery Pulmonary function Outcomes  Pulmonary function Outcomes  Restrictive impairment (n=3) (TILC OR FVC <75%) Bleomycin only vs Bleomycin only solution on	Study  No. of participants (median/mean, range) yr chemotherapy  Mulder 2011 193 CCS Median 17.9 Bleomycin plus surgery 1.6% (n=3) (n=3) (n=98)  Bleomycin only 50.8% (n=98)  Hard 1 retrospective cohort study  1 retrospective cohort study  Thoracic surgery Pulmonary function Outcomes  Pulmonary function Outcomes  Effect size  Odds Ratio (95%CI)  Bleomycin plus surgery 1.6% Restrictive impairment (TLC OR FVC <75%) Bleomycin plus surgery vs. Bleomycin only vs Bleomycin only vs Bleomycin only sonly  Bleomycin only 50.8% Not estimable as no cases in Bleomycin + surgery  Tretrospective cohort study  1 retrospective cohort study  One study only	Study  No. of participants (median/mean, range) yr chemotherapy  Mulder 2011 193 CCS Median 17.9 Bleomycin plus (m=3) (m=3) (m=98)  Bleomycin only 50.8% (n=98)  Herrospective cohort study -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 One study only  Thoracic surgery combined with pulmotoxic chemotherapy (bleomycin, CCNU, BCNU, Busulfan, Cyclophos PFT quality)  Thoracic surgery pulmonary function Outcomes  PFT quality  Pulmonary function Effect size PFT quality  Outcomes  PFT quality  Odds Ratio (95%Cl) 1. No Bleomycin plus surgery vs. Bleomycin plus surgery vs. Bleomycin plus surgery vs. Bleomycin only only 4. No Not estimable as no 6. No cases in Bleomycin + surgery  +4 1 retrospective cohort study -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

**Pulmonary function** 

**Outcomes** 

**Effect size** 

**PFT quality** 

Risk of bias

**Thoracic Surgery** 

and

	PIC	0	Study	No. of participants	Follow-up (median/mean, range) yr	and	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
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(1 study; 193 participants; 3 participants exposed to thoracic surgery and bleomycin; 98 participants exposed to bleomycin only)

No statement possible on restrictive abnormalities (TLC, FVC) after thoracic surgery combined with bleomycin vs. bleomycin alone in CAYA cancer survivors.

10a What is the risk of <a href="https://hyperinflation">hyperinflation</a> after thoracic surgery combined with pulmotoxic chemotherapy (bleomycin, CCNU, BCNU, Busulfan, Cyclophosphamide, Methotrexate, Gemcitabine)?

Very small sample size exposed to thoracic surgery and bleomycin, no effect size, PFT quality is unsure.

No study

Precision:

Effect size:

Conclusion:

Comment

Publication bias:

<u>Dose-response:</u> <u>Plausible confounding:</u>

Quality of evidence:

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 diffusion capacity impairment 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: Study design: Study limitations: Consistency: Directness: Precision: Publication bias: Effect size: Dose-response: Plausible confounding	sessment:  ign: +4 1 retrospective cohort study tations: -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 cy: 0 One study only c: -1 Results are broadly generalizable. PFT quality is unsure (no reference values and guidelines mentioned)2 Results shown with effect size but large confidence interval, one study only c: 0 Unlikely c: 0 No large magnitude of effect onse: 0 Not applicable									
Quality of evidence: Conclusion:	No si one s	⊕⊖⊖ Very low  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 obstructive abnormalities after thoracic surgery combined with	Stone 2020 (19)	62 high-risk neuroblasto ma	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
<u>Directness:</u>	O 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
<u>Dose-response:</u>	0 Not applicable
Plausible confounding:	0 No evidence of possible confounding
Quality of evidence:	$\oplus \ominus \ominus \ominus$ 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 restrictive abnormalities 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 neuroblasto ma	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	OR, 95%CI 14.00 (1.68 – 116.85), p=0.003	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
					TLC (TLC <80% pred) RT + Surgery yes: 75.0% abnormal RT + Surgery no: 34.0% abnormal	5.82 (1.39 – 24.38), p=0.010		
GRADE assessment	<i>:</i>							
Study design: Study limitations:	+4 -1			rospective cohort stud ow in 1/2, high in 1/2	dy ; Attrition bias low in 2/2; De	etection bias low in 1/2, ur	nclear in 1/2; Confo	ounding high in 1/2low in
Consistency:	0		show an increased r					
<u>Directness:</u>	-1				L/2 reference values and guid	delines mentioned).		
Precision:	-1 0		n with effect size bu	it very large confidence	ce intervals			
Publication bias: Effect size:	+1	Unlikely Large magnitu	ide of effect					
Dose-response:	0	Not applicable						
Plausible confoundi			of possible confound	ding				
Quality of evidence	:	O VERY LOW						
Conclusion:	expos (2 stu	ure to thoracic	surgery and radioth	erapy exposing lung t	racic surgery combined with issue in CAYA cancer survivo nerapy exposing lung tissue p	ors.		•
Comment		· · · · · · · · · · · · · · · · · · ·	sample size expose	ed to thoracic surgery	and radiotherapy exposing I	lung tissue, very large conf	fidence interval. Di	fferent comparators

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>hyperinflatio</u>	<u>n</u> after thoracic	surgery combined	with radiotherapy ex	posing 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 diffusion capacity impairment 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 neuroblasto ma	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: Study design: Study limitations:  Consistency: Directness: Precision: Publication bias: Effect size: Dose-response: Plausible confoundi	+4 -1 0 -1 -1 0 +1	Some limitation 1/2 Both studies sho Results are broa Results shown v Unlikely Large magnitud Not applicable	s: Selection bias low ow an increased risl idly generalizable. F vith effect size but l	k, one with a significal PFT quality differs (1/2 large confidence inter	Attrition bias low in 2/2; Dete nt effect 2 reference values and guide		lear in 1/2; Confo	unding, low in 1/2, high in
Quality of evidence Conclusion:	Incre expos (2 stu not e	→ VERY LOW ased risk for difficure to thoracic sidies; 255 particic xposed to thoracic	usion capacity impa surgery and radioth pants; 28 participa sic surgery and radi	irment (DLCO) after t erapy exposing lung t nts exposed to radioth otherapy exposing lur	horacic surgery combined wissue in CAYA cancer survivo nerapy exposing lung tissue ang tissue ang tissue) herapy exposing lung tissue,	rs and thoracic surgery; 98 pa	articipants expose	

# 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 obstructive abnormalities 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 Study design: Study limitations: Consistency: Directness: Precision: Publication bias: Effect size: Dose-response: Plausible confound Quality of evidence	+4 -2 0 0 -2 0 0 0 0	Some limitations: S One study only Results generalizab Important imprecis	Selection bias low in ole. PFT quality is go sion; only one study e of effect	• •	w in 1/1; Detection bias hig and guidelines mentioned e	, ,	g high in 1/3	
Conclusion:	Dec can (1 st	reased risk for obstru cer survivors	21 participants exp	osed to chemotherap	rapy exposing lung tissue or			

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 restrictive 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)	Restrictive impairment	Odds Ratio (95%CI)	1. No 2. No	Retrospective cohort SB: low risk
			( /	( ,	(TLC OR FVC <75%)	Radiotherapy plus	3. No	AB: low risk
				Bleomycin plus		bleomycin vs.	4. No	DB: unclear
				radiotherapy		Bleomycin only	5. No	CF: low risk
				4.7% (n=9)		9.41 (1.71-51.86)	6. No	
GRADE assessmen	t:							
Study design:	+4	2 retrospective	cohort studies					
Study limitations:	-2	Some limitation	s: Selection bias low	in 2/2; Attrition bias l	ow in 2/2; Detection bias hi	gh in 1/2, unclear in 1	/2; Confoundin	g high in 1/2, low in 1/2
Consistency:	0	Both studies sho	ow tendency to restri	ctive abnormalities				
<u>Directness:</u>	-1		-		stated reference values, ½ s	-		
Precision:	-1	Important impre	ecision, 1/2 with very	wide confidence inte	erval, in 1/2 precision canno	t be judged as result s	hown as p-valu	ie only
Publication bias:	0	Unlikely						
Effect size:	+1	Large magnitude	e of effect					
<u>Dose-response:</u>	0	Not applicable						
Plausible confound	ling: 0	No evidence of	possible confounding					
Quality of evidence	e: ⊕⊖	⊖⊖ Very low						
Conclusion:	Incre	ased risk for restr	ictive abnormalities (	TLC or FVC) after radi	otherapy exposing lung tiss	sue combined with ble	omycin vs. blec	omycin alone in CAYA cancer
	survi	vors						
	(2 stu	udies; 1 study sign	ificant, 1 study non-s	ignificant; 234 partici	pants; 30 participants expo	sed to chemotherapy	and radiothera	py exposing lung tissue )
Comment	Impo	ortant imprecision,	, PFT quality unsure,	small sample size exp	osed to chemotherapy and	radiotherapy exposing	g lung tissue; or	ne study focusses on
	bleoy	ymcin-containing	chemotherapy the se	cond does not differe	entiate between type of che	motherapy		

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>hyperinflatio</u>	<u>n</u> after pulmotoxic che	emotherapy combin	ed with radiotherap	y 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	Bleomycin only		Odds Ratio	1. No	Retrospective cohort
			(5.6-36.8)	50.8% (n=98)	Diff	(95%CI)	2. No	SB: low risk
				Dia a manaira mina	Diffusion impairment	Bleomycin only vs	3. No	AB: low risk
				Bleomycin plus	(DLCO <75%)	radiotherapy +	4. No 5. No	DB: unclear CF: low risk
				radiotherapy 4.7% (n=9)		bleomycin	6. No	CF. IOW TISK
				4.7% (11-3)		6.17 (1.37-27.84)	O. NO	
GRADE assessment	::							
Study design:	+4	2 retrospective	cohort studies					
Study limitations:	-2	Some limitation	ns: Selection bias lov	in 2/2; Attrition bias	low in 2/2; Detection bias	high in 1/2, unclear in	1/2; Confoundi	ng high in 1/2, low in ½
Consistency:	0	Both studies sh	ow tendency to diffe	usion capacity impairr	ment			
<u>Directness:</u>	-1	•	•	• • • •	stated reference values, 3	,	•	
Precision:	-1	Important impr	recision, 1/2 with ve	ry wide confidence int	terval, in 1/2 precision can	not be judged as result	shown as p-val	ue only
Publication bias:	0	Unlikely						
Effect size:	+1	Large magnitud	le of effect					
<u>Dose-response:</u>	0	Not applicable						
Plausible confoundi			possible confoundir	g				
Quality of evidence		⊖⊖ Very low						
Conclusion:			ion capacity impairn	nent abnormalities af	ter radiotherapy exposing	lung tissue combined v	vith bleomycin v	vs. bleomycin alone in CAYA
		r survivors.						
	(2 stu	dies; 1 study signi	ficant, 1 study non-s	ignificant; 234 partici	pants; 30 participants expo	sed to chemotherapy	and radiotherap	oy)
Comment	•	•			osed to chemotherapy and	I radiotherapy; one stu	dy focusses on	bleoymcin-containing
	chem	otherapy the seco	and does not differer	ntiate between type o	f 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 assessmer	nt:							

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
<u>Directness:</u>	O 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:	significant effect on reduced risk for obstructive abnormalities (FEV1) CAYA cancer survivors with a smoking history compared to those without.
	study; 62 participants; 11 former or current smoker)
Comment	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
risk of restrictive abnormalities in CAYA who have a history of	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	OR, 95%CI 0.69 (0.19 – 2.53), p=0.569	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
tobacco exposure compared to CAYA with no history of tobacco exposure					TLC (TLC <80% pred) Smoke yes: 36.4% abnormal Smoke no: 43.1% abnormal	0.75 (0.20 – 2.90), p=0.748		
GRADE assessment								
Study design:	+4	1	•	to 4/4. Association lateral	in 4/4 Bahartian bias l		lta a btab ta 4/4	
Study limitations:	-2		Selection bias high	in 1/1; Attrition bias i	ow in 1/1; Detection bias l	ow in 1/1; Confound	ling high in 1/1	
Consistency: Directness:		One study only Results broadly go	eneralizable DET co	and (references stated	lung function procedure	mentioned)		
Precision:	-:			e with 95%CI), only one		inentioned)		
Publication bias:		0 Unlikely	A COISION (CITECT SIZE	. with 55/001, only one	Juay			
Effect size:		0 No large magnitu	de of effect					
Dose-response:		0 No dose-response						
Plausible confoundi	ing:		ossible confounding					
Quality of evidence	:	O Very low						
Conclusion:	No sigi				'C, TLC) CAYA cancer survi	vors with a smoking	history compared t	to those without.
Comment	One st	udy only, small samp	le size, only neurob	lastoma survivors				

PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Tobacco exposure	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias	
	he risk of hyperintla	tion in CAYA who have	a history of tobacco	exposure compared t	o CAYA with no history of	tobacco exposur	e		
No study									
PICO	Study	No. of	Follow-up	Tobacco exposure	Pulmonary function	Effect size	PFT quality	Risk of bias	

PICO	Study	No. of participant	Follow-up ts (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-ris neuroblast	k Median 5.29	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 assessmen	it:											
Study design:		•	ive cohort study	4 /4	lauria 4/4 Dataatia III		lin - lei - le i - 4 /4					
Study limitations:				in 1/1; Attrition bias	ow in 1/1; Detection bias	low in 1/1; Confound	ing nign in 1/1					
Consistency:		0 One study	•		f							
Directness:				•	, lung function procedure	mentioned)						
Precision: Publication bias:		-1 No importa 0 Unlikely	ant imprecision (effect size	e with 95%tij, only on	e study							
Effect size:		•	agnitude of effect									
Dose-response:			esponse relationship									
Plausible confound	ling.		esponse relationship se of possible confounding	7								
Quality of evidence		O No evident	c or possible comountains	5								
Conclusion:	N	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	Follow-up	Tobacco exposure	Pulmonary function	Effect size	PFT quality	Risk of bias
		participants	(median/mean,		Outcomes			
			range) yr					

11a What is the	Oancea 2014	433 CCS	>10 yrs from	a. Never Smoker:	% predicted median	Comparison	1. No	Retrospective cohort
risk of	(25)		diagnosis	62% (n=269)	(IQR)	with never	2. No	SB: high risk
<u>obstructive</u>				b. Former: 18%		smoker as ref.,	3. No	AB: low risk
abnormalities in				(n=80)		using the DSCF	4. Yes: ATS	DB: low risk
smokers/ex-				c. Current: 19%	FEV1/FVC	procedure	5. No	CF: unclear
smokers				(n=84)	a. 1.02 (0.96-1.06)		6. No	
compared to				d. Ever smoker	b. 0.98 (0.93-1.04)	p=0.01		
non-smokers?				<6PY (n=69)	c. 1.00 (0.94-1.04)	p=0.03		
				e. Ever smoker ≥6PY	d. 1.00 (0.94-1.04)	p=0.38		
				(n=80)	e. 0.99 (0.92-1.03)	p=0.005		
					FEV1			
					a. 79.0 (69.0-92.0)			
					b. 76.5 (65.5-86.0)	p=0.23		
					c. 79.5 (67.0-89.0)	p=0.83		
					d. 79.0 (69.0-88.0)	p=0.66		
					e. 78.0 (66.0-87.0)	p=0.38		
GRADE assessmen	it:							
Study design:	+	4 1 retrospective	cohort study					
Study limitations:		2 Some limitation	s: Selection bias high	n in 1/1; Attrition bias hi	gh in 1/1; Detection bias	low in 1/1; Confound	ding unclear in 1/1	
Consistency:		One study only						
<u>Directness:</u>	-	· ·	~	•	erences stated, lung func	•	•	
Precision:			ecision, precision car	nnot be judged because	results shown as p-value	only, only one study	1	
Publication bias:		0 Unlikely						
Effect size:		0 No large magni						
<u>Dose-response:</u>		0 No dose-respon	•					
Plausible confound			possible confounding	g				
Quality of evidence		⊖⊖ Very low						
Conclusion:					former smoker and those	e wno smoked ≥6 PY	vs. never smokers	n CAYA cancer survivors.
			; 164 former or curre	ent smoker)				
Comment	Impor	tant imprecision, PF	I 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 restrictive abnormalities in smokers/exsmokers 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

				( 00)				
				(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%Cl, 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	Logistic regression Odds Ratio (95%CI) 0.9 (0.7-1.9)	1. Yes 2. No 3. No 4. Yes: ATS 5. No	Prospective cohort SB: Low risk AB: low risk DB: low risk CF: high risk
					≥80% predicted)		6. Yes	Ci i ingli risk
GRADE assessmen Study design: Study limitations:	+-	2 Some limitations unclear 1/3	: Selection bias higl	ospective cohort studies n in 2/3, low in 1/3; Attr		etection bias low in 2/3	s, unclear in 1/3; Confo	unding high in 2/3,
Consistency: Directness: Precision: Publication bias: Effect size: Dose-response: Plausible confounce	-: -: ( ( NA	<ol> <li>Important impre</li> <li>Unlikely</li> <li>No large magnitu</li> <li>No dose-respons</li> </ol>	generalizable but ur cision, 2/3 with sma ude of effect	nsure PFT quality (1/3 st all confidence intervals,				nly
Quality of evidence Conclusion:	No sig			es (TLC, FVC, "restrictive urrent or former smoke		vivors who smoke/smok	xed compared to non-s	moker.
Comment				no smoke/smoked. PFT	<u> </u>	rent definitions for "res	trictive".	

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 th	e risk of <u>hyperinfla</u>	<u>tion</u> in smokers/ex-sn	nokers 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/exsmokers 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 (-16.03.6, 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:

Study limitations:

<sup>+4 1</sup> retrospective cohort study, 1 prospective cohort study, 1 prospective cross-sectional study, 1 retrospective cross-sectional study

<sup>-2</sup> 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
<u>Directness:</u>	-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:	$\oplus \ominus \ominus \ominus$ 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)	Tobacco exposure	Pulmonary function Outcomes	Effect size	Risk of bias
			yr				
11b What is the risk	associated with diffe	rent doses (pa	ck-years)?				

#### No study

### 11c Environmental tobacco smoke

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

### No study

## 11d Marijuana

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

No study