S-Table -1: Study details for reported dosimetric correlates

1st author[#] inst, calc algorithm [Reference #]	Lung definition	# dosimetrically evaluable treatments /Total # pts	Median Follow-up (months)	Grading in paper	% total with G2+ RILT	% total with G3+ RILT	Median (m) or Mean (M) Rx [range]	^ Median (m) or Mean (M) fractions [range]	Biological Correction	Significant D/V variables or cutpoints	Comments
Allibhai[S, P] [25]	Bilateral lungs, 4DCT for target definition, free-breathing; otherwise not specified	185	15.2 [6-76]	CTCAE3.0	17.9% of 52 pts with T2 tumors; 4.4% of 133 pts with T1	1.8 % (none > Grade 3)	Not enough information to determine. Multiple regimens used: 50 Gy in 10 fx, 60 Gy in 8, %0 Gy in 5, 52.5 Gy in 5, 48 in 4, 54 in 3, 60 Gy in 3)	Not enough information to determine.	N	None found, though V_{20}, MLD investigated.	Focus of paper is on effect of GTV size. GTV and PTV significantly correlated with G2+ RP but not G3+ RP
Bahig [S, PB or CS] [36]	Bilateral lungs, 4DCT Free-breathing; GTV subtracted following STARs trial	504 (28 with pre-existing ILD*^)	24 [2-49]	CTCAE3.0	Not Stated	4% of total (1% G5 RP)' 32% in ILD pts vs 2% in non_ILD	180 G (M) [72-180]	Constraints followed STARS protocol: 50 GY/4 fx for central, 54 Gy/3 fx peripheral. But fraction numbers likely differed (reported BED range 72-180 Gy_{10}	LQ for Rx but probably not DVHs	V_5 28% [21-42%} with G3+ RP, 18% [14-22%] no G3+ RP MLD 7 Gy [5-9 Gy] with RP, 4 Gy [3-5 Gy] no RP	Effect of ILD*^ on RP incidence highlighted; ILD highly significant predictor of G3+ RP (p=0.001)
Baker [S, PB or CS] [37]	Bilateral lungs, 4DCT; Lungs_minus iGTV^^^	236/263 (> 6 m followup)	At least 6 m Pts treated multiple times had median FU 15.6 m [3-58.7]	CTCAE3.0	12.3%	1.3%	50 Gy (m)[40-60]	5 (m)[4-8]	N	Univariate: V_5, V_{13}; $V_{\_prescription}$ for Rx dose=60 Gy; V_{20} trend No dosimetric variable survived multivariate	advised bilateral lung V_{20}<10%,MLD below 5-6 Gy
Barriger [S, None (70%), HND (30%)] [38]	Bilateral lungs minus GTV	143/251	17 [0.3-89]	CTC 2.0	9.2% of total #, 10.5% of those with dosimetry.	2.4% of total number, 2.1% of those with dosimetry	60 Gy (m) [24-72]*[1]	3 (m) [3-5]	N	Univariate only: median splits for MLD, V_{20}	** Significant median splits: MLD= 4 Gy V_{20}= 4%

Borst[S* CS] (2009) [26]	Bilateral lungs minus GTV	175 /128[*2]	16.1 m: all RP occurred within 6.2 m after tx	CTC 2.0 or SWOG	10.9%	0.8%	48 Gy (m^{*3})[25-60]	4 (m^{*3}) [4-16]. Note 167 treatments were 4 or 8 fractions	Y (LQ, α/β =3 Gy)	Lyman Model[&] on MLD2 (n=1)	MLD is defined as the NTD (or EQD2) with α/β =3 Gy; This study found no significant difference between the MLD model parameters for SBRT and conventional fractionation.
Borst[S* CS] (2010) [39]	Same cohort as 2009	same cohort as Borst 2009	same cohort as Borst 2009	CTC 2.0 or SWOG	10.9%	0.8%	48 Gy (m^{*3}) [25-60]	4 (m^{*3}) [4-16]. 167 treatments were 4 or 8 fractions	Y (LQ and LQL)	Lyman models [&]on Mean NTD and $V_{\_NTD}$ (NTD calculations using LQ and LQL) $V_{\_NTD}$ model parameters given in Table 1 of citation	Best fit α/β = 3 Gy. LQ fit better than LQL, but LQL within the LQ model's 95% CI. See also Figure 3 of this report
Chang[S, P] (2012) [40]	Bilateral lungs minus GTV[*4] or treated lung minus GTV when ipsi metrics are evaluated; 4DCT for all plans	130/130	26 [6-78]	CTCAE 3	11.5%	2.3%	50 Gy (all)	4 (all)	N	Dichotomized at median values: Univariate for MLD and V_5-V_{40} for bilateral lung and ipsi lung Multivariate: Ipsilateral MLD Multivariate with onset time included (Cox regression) : Ipsilateral V_{40}	MLD: Significant medians are 5.05 Gy (total lung, univariate) and 9.14 Gy (ipsi lung; uni and multivariable). V_{dose}: Significant medians for V_{5-40} for total and ipsilateral lung (see Table 4 of reference and Figure 4 of this report)
# Chang[S, P] (2014) [41]	Bilateral lungs minus GTV[*4]; 4DCT	100 (all central location)	30.6 [9.4-92.6]	CTCAE3	12%	1%	70 Gy (18 pts); 50 Gy (82 pts)	10 fx (18 pts); 4 fx (82 pts)	N	For patients receiving 4 fractions - Univariate: Bilateral lung MLD, V_5, V_{20}; Ipsilateral lung MLD, V_{10}, V_{20} Multivariate: Total lung MLD, V_{20} Ipsi lung V_{30}	&& Significant cutpoints for the 4-fraction cases: Univariate whole lung: MLD=6 Gy; V_5=30%, V_{20}=12%. Univariate ipsi lung: MLD=10 Gy, V_{10}=35%, V_{20} =25%: Multivariate: Lung MLD=6 Gy, Lung V_{20}=12%, ipsiV_{30}=15%
Duncker-Rohr[S, CS] [42]	Not stated but mean bilateral lung doses referenced	45/39	17	CTCAE4 (acute) and RTOG/ EORTC (late)	10.2%	0	35 Gy (m) [21-37.5]	5 (m) [3 or 5]	N	No formal dose-volume analysis but median bilateral MLD with symptomatic RP is 4.79 Gy, without RP is 3.01 Gy	
Grills[Mu, P] [43]	Bilateral lungs nn k ot GTV	505/483	15.6 [1.2-87.6]	CTC Vn 3	7%	2%	54 Gy (m)[11-64]	3 (m) [1-15]	Y for some variables	## V_{20},MLD and BED3 investigated but were not significant	

Guckenberger[S, CS] [44]	Ipsilateral lung not CTV; 4DCT	75/59	13	SWOG	16%	0	37.5 Gy (m) [30-48]	3 (m) [1-8]	Y	Probit model for Ipsilateral MLD2 (α/β=3 Gy) Ipsilateral lung $V_{2.5}$ was 41.4±8% for patient with and 30.5±13.8% for patients without RP	Model parameters (95% CI) in reference: TD50=32.4 (20.3-85.5) Gy; m=0.67 (0.49-1.03). Also model parameters for NTCP probit model of $V_{2.5}$: 50% value is 62.3 % (95% CI 49.9-84.1%) , m=0.44 (95% CI 0.31-0.66) See Figure 3 of this report.
Hayashi [S, E(Batho)] [45]	Bilateral Lungs; subtraction not mentioned. Breath-hold (or 3 phases for target definition)	81	29 [5-84]	CTCAE4	11.1%	2.5%	48 Gy in 4 fx for 60 pts, 60 in 10 fx for 21 pts	4 (m) [Either 4 or 10]	N	Univariate: MLD split at 4.8 Gy, [range 2.9-6.9] V_{20} split at 6.8% near significant on univariate, [range 3.7-11.1%] Multivariate: MLD and V_{20}	Median MLD Gr 0-1: 3.75 Median MLD Gr 2-3: 4.8 Median V_{20} Gr 0-1: 5.1 Median V_{20} Gr 2-3: 6.8 Age significant (older age worse) Fractionation not significant
Inoue[S, NS] [11]	Bilateral lung (no subtraction mentioned); 4DCT	189/87 63 pts had multiple GTVs	Not stated	NCI-CTC	16% at 1 yr; 30% at 2 yr (simple addition of KM curves}	4% at 1 yr, 10% at 2 yr	EQD2 88 Gy (m) with α/β=10 Gy (EQD2 25-140)	4 (m) [4-10]	Y	No formal dose-volume analysis	^^ Only V_{EQD2_20} examined; α/β and significance not stated. All tumors were metastatic Quoted lung metrics are based on cumulative lung doses for treatment of all the patient's GTVs
Kimura[S, P] [12]	Long scan or end-exhale. Bilateral lungs	52/45 with >6 months follow-up	18 [6-56]	CTCAE 3.0 and CT imaging	46.8%	6.4%	60 Gy (m) [48-60]	8 (m) [4-14]	N	Focus was CT changes for patients with/without emphysema. V_{20} and dose/fraction correlation sought but not found	
Kundu[S, E (NS)] [17]	free-breathing; V_dose dosimetry on "lung not PTV"; MLD on 'air inflated parenchyma', so	8/8	18 [8-44]	RTOG	12.5%	12.5% (1 pt, steroids, RTOG)	48 Gy (all)	6 for 5 peripheral; targets; 8 for 3 central targets	N	Table of dose-volume metrics given but the RP case is not distinguished	

	bilateral lungs'										
Li[S, P] [22]	Not stated[*4] but probably bilateral lungs_not_GTV; 4DCT based on previous work from this group	82/82	21.1 [12-80.1]	Not stated but probably CTCAE 3 based on previous work from this group [*4]	17%	2.4%	70 Gy (all)	10 (all)	N	V_{40} total lung on Univariate; no other D/V metrics (looked at MLD, $V_{10,20,30,40}$ for total and ipsi lung); no D/V metric on Multivariate	Recommended MLD<9 Gy; V_{40}<7% for total lung ; For V_{40}, symptomatic RP was 12% below, 40% above.
Matsuo[Mu, E (AAA)] [46]	Slow CT; bilateral lungs not PTV	74/74	31.4 [4.2-65]	CTCAE3	20.3%	1.4%	48 Gy (all)	4 (all)	N	Significant: V_{20},V_{25} Trend: V_{10}, V_{15},V_{30}, V_{35}, V_{40}	V_{20} =5.8% (G2+ RP below is 15%, 42.9% above)) V_{25} =4.2% (G2+ RP below is 14.8%, 46.2% above)
Ong[S, E (AAA)] [18]	Average Intensity Projection; Bilateral lungs not PTV; ipsi lung not PTV	18/18	12.8	CTCAE 4	28%	11%	60 Gy in 8 fx (10 pts) , 55 Gy in 5 fx (8 pts)	8 fx (10 pts) and 5 fx (8 pts)	N	Paper gives outcomes graph for total lung $V_{5,10,15,20}$ and MLD: also ipsi and contra V_5	No RP observed for total lung V_5 below 37% and contralateral lung V_5 below 26%:; See Figure 3 in this report
Ohashi[S, NS] [47]	Quiet breathing, lung definition not specified	17/15	Not stated but patients had pulmonary Fn tests at 1 yr	CTCAE2.0	Not stated	86.7% had 'no respirator symptoms of more than Grade 2'	50 Gy (m) [40-60]	5 2 had prior conventional RT	N	Focus on PFT changes (no dosimetric correlation here), no RILT analysis. Typo in description of V_{20} vs RP	Median V_{dose} values given but not related to outcome

Ricardi [S, CC] [48]	Ipsilateral lung not CTV	63/60	30.9 [6.7-56.7]	RTOG	14.3%	Grades 2 and 3 not separated; no higher Grade than 3	45 Gy in 3 fx for 58 tumors, 26Gy in 1 fx for 5	3 for 58 tumors, 1 for 5	Y (LQ, EQD2 with α/β=3 Gy)	Ipsilateral MLD2 statistically significant (t-test and logistic regression) to differentiate G2+ RP from non-symptomatic cases. Mean MLD2 for Grades 0-1 RP was 11.2 Gy (95% CI 10.1-12.3 Gy) and for 2-3 RP, mean MLD2 was 20.3 Gy (95% CI 16.6-223.9 Gy) Paper also presents two models using ipsilateral MLD2 : Lyman model with original LKB parameters and a logistic regression model (parameters given in paper)	See Section 6 and Figure 3 in this report for further discussion of models.
Stauder[S, E (ND)] [49]	4DCT for ITV definition; not otherwise described though values of MLD and Vdoses imply bilateral	88/84	15.8 [2.5-28.6]	CTCAE3.0	12.5%;	3.4 %	48 Gy (m) [32-60]	4 (m) [3-5]	N	Investigated lung variables MLD, V_{20}, V_{13}, V_{10}: none were significant. Only significant dose variable was PTV Dmax> 60 Gy	
Takeda[Mu, CC] [27]	Slow CT; bilateral lungs (target subtraction not stated)	133/128	12 [6-45]	CTCAE 3	21%	5%	50 Gy (m) [3 dose groups: 40, 50, 60]	5 (all but 4 cases)	N	V_5 through V_{25} and MLD distinguish G2 RP from G0-1 RP; V_{15-30} distinguish G2 RP from G3 RP. No dosimetric or clinical factors distinguish G3 RP from G0-1 RP.	Curves (Fig 3 in reference) for 5% and 15% G2 RP risk vs V_{dose}; Risk<15% for V20<6.5%
Westover[S] [50]	30% phase of 4DCT; no other information	20/15	24.1	CTCAE V4.03	5%	5%	45 Gy RBE (m) (42-50)	3 for 17/20 tumors	N	None sought;	Protons; 4 pts had prior RT Only lung toxicity is one G3 RP

Yamashita[S, CC] [51]	Slow scan: Bilateral lungs, no subtraction stated	117	14.7 [0.3-76.2]	CTCAE3.0	not stated	Not stated (7.7 % RILT 4 or 5)	48 Gy (all)	4 (all)	N	V_{20}, MLD not significant. Pre-treatment Serum KL-6, and Surfactant Protein D (SP-D) were significant biomarkers; Pre-tx Interstitial Pneumonitis (IP) was a significant risk factor.	

Shaded studies contributed to Figure 4

Superscript S for single institution, Mu for 2 or more. When there are only two dose/fractionation groups they are separately listed

Dose calculation algorithm: PB=pencil beam, P=Pinnacle, E=Eclipse (algorithm mentioned if described), CS=Convolution/superposition, CC=Collapsed Cone, HND=inhomogeneity done but not described, NS=not stated whether inhomogeneity correction done

Note: Many studies used 4DCT for target definition but how or if this was used for OAR definition is seldom stated.

*^: ILD is Interstitial Lung Disease.

^^^: iGTV is union of GTVs from 4DCT or at minimum end-inhale, end-exhale and planning scan

*[1:] Only a wide range of doses specified for 13% patients

**: Significant Splits: G2+ RILT was 4.3% if MLD<4 Gy, 17.6% if MLD>4 Gy. G2+ RILT was 4.3% if V_{20}<4%, 16.4% if >4% S*: All hypofractionated patients treated at one institution, conventionally fractionated at another

*[2 :] 95 pts had one target. 20 patients had multiple sites treated with a single treatment plan (42 targets). 13 patients had 2 or more treatments delivered with different plans, separated by 0 to > 13 months (38 targets). Evaluation was done for the summed plans

*[3:] Median over all treatments (details in tables 1-3 of citation). Single lesion case doses ranged from 35-60 Gy in 4 or 8 fractions.

& : Mean NTD (EQD2) from LQ with α/β=3 Gy (TD50=19.6 Gy, m=0.43); RP incidence was compared with n=1 Lyman model for conventionally fractionatedseries

*[4]: Lung definition is bilateral lungs-GTV.

#: Chang 2012 has only 11 central lesions; Chang 2014 is 100 central lesions; these studies share few (if any) patients.

&&: Incidence of G2+ RP almost 2 times higher if bronchial tree Dmax>38 Gy, V_{35}>1cc.

##: How BED3 was applied was not described

^^: $V_{20}\leq$30% was suggested; 30% is large compared to the other reviewed report

S-Table-2a: Radiation induced lung toxicity grading systems [45]

System	Grade 1	Grade 2	Grade 3	Grade 4
RTOG/EORTC Acute Lung	Mild symptoms of dry cough or dyspnea on exertion	Persistent cough requiring narcotic, antitussive agents / dyspnea with minimal effort but not at rest	Severe cough unresponsive to narcotic antitussive agent or dyspnea at rest / clinical or radiological evidence of acute pneumonitis / intermittent oxygen or **steroids** may be required	Severe respiratory insufficiency / continuous oxygen or assisted ventilation
RTOG/EORTC Late Lung	Asymptomatic or mild symptoms (dry cough) Slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough) Low grade fever Patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis Dense radiographic changes	Severe respiratory insufficiency/ Continuous O_2/ Assisted ventilation
SWOG Acute Lung	Radiographic changes; Symptoms do not require steroid	Radiographic changes; require **steroid**, or tap of effusion	Radiographic changes; require oxygen	Radiographic changes; require assisted ventilation
SWOG Late Lung Fibrosis	Radiographic changes; No symptoms	Not specified	Radiographic changes; with symptoms (also code the symptoms)	Not Specified

CTCAE 3.0 Pneumonitis/ Infiltrates	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL, Oxygen indicated	Life-threatening, ventilatory support indicated
CTCAE3.0 Pulmonary fibrosis (radiographic changes)	Minimal radiographic findings (or patchy or bi- basilar changes) with estimated radiographic proportion of total lung volume that is fibrotic of <25%	Patchy or bi-basilar changes with estimated radiographic proportion of total lung volume that is fibrotic of 25 – <50%	Dense or widespread infiltrates/consolidation with estimated radiographic proportion of total lung volume that is fibrotic of 50 – <75%	Estimated radiographic proportion of total lung volume that is fibrotic is ≥75%; honeycombing
CTCAE 4.03 Pneumonitis (A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma)	Asymptomatic; clinical or diagnostic observations only; Intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)
CTCAE 4.03 Pulmonary fibrosis (A disorder characterized by the replacement of the lung tissue by connective tissue, leading to progressive dyspnea, respiratory failure or right heart failure)	Mild hypoxemia; radiologic pulmonary fibrosis <25% of lung volume	Moderate hypoxemia; evidence of pulmonary hypertension; radiographic pulmonary fibrosis 25 - 50%	Severe hypoxemia; evidence of right-sided heart failure; radiographic pulmonary fibrosis >50 - 75%	Life-threatening consequences (e.g., hemodynamic/pulmonary complications); intubation with ventilatory support indicated; radiographic pulmonary fibrosis >75% with severe honeycombing

All: Grade 0=no symptoms, Grade 5=toxicity directly related to death

S-Table-2b: RTOG-EORTC Lent Soma Scale [46]

	GRADE 1	GRADE 2	GRADE 3	GRADE 4	SCORING
Subjective					
Cough	Occasional	Intermittent	Persistent	Refractory	____ **Instructions**
Dyspnea	Breathless on intense exertion	Breathless on mild exertion	Breathless at rest, limits all activities	Prevents any physical activity	____ **Score the 8 SOM parameters with 1 - 4**
Chest pain/discomfort	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory & excruciating	____
Objective					
Pulmonary fibrosis	Radiological abnormality	Patchy dense abnormalities on radiograph	Dense confluent radiographic changes limited to radiation field	Dense fibrosis, severe scarring & major retraction of normal lung	____ **(Score = 0 if there are no toxicities)**
Lung function	10% - 25% reduction of respiration volume and/or diffusion capacity	> 25% - 50% reduction of respiration volume and/or diffusion capacity	> 50% - 75% reduction of respiration volume and/or diffusion capacity	> 75% reduction of respiration volume and/or diffusion capacity	____ **Total the scores and divide by 8**
Management					
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention	____ **LENT Score:**
Cough		Non-narcotic	Narcotic, intermittent corticosteroids	Respirator, continuous corticosteroids	____ _____
Dyspnea		Occasional O_2	Continuous O_2		____

Analytic					
PFT	Decrease to >75% - 90% of preTx value	Decrease to >50% - 75% of preTx value	Decrease to >25% - 50% of preTx value	Decrease to ≤ 25% of preTx value	Y/N Date:
DLCO	Decrease to >75% - 90% of preTx value	Decrease to >50% - 75% of preTx value	Decrease to >25% - 50% of preTx value	Decrease to ≤ 25% of preTx value	Y/N Date:
% O_2/CO_2 saturation	> 70% O_2, ≤ 50% CO_2	> 60% O_2, ≤ 60% CO_2	> 50% O_2, ≤ 70% CO_2	≤50% O_2, >70% CO_2	Y/N Date:
CT/ MRI	Assessment of lung volume and zones of fibrosis				Y/N Date:
Perfusion scan	Assessment of pulmonary blood flow and alveolar filling				Y/N Date:
Lung lavage	Assessment of cells and cytokines				Y/N Date:

S-Table-3: Dose constraints of lung from individual NRG/RTOG trials

	Number of Fractions	Structure	Constraint (no deviation)	Comments
RTOG 0813	5	Lung_not_GTV	D_1500cc <= 12.5 Gy	Dose calculation algorithm must be credentialed
			D_1000 cc<=13.5 Gy	
RTOG 0915	1	Lung_not_GTV	D_1500 cc <=7 Gy	Dose calculation algorithm must be credentialed
			D_1000 cc <=7.4 Gy	
	4		D_1500 cc <=11.6 Gy	
			D_1000 cc <=12.4 Gy	
RTOG 0618	3	Lung_not_GTV	%V20<=10% (minor deviation up to 15%)	No inhomogeneity correction
RTOG 0236	3	Lung_not_GTV	%V20<=10% (minor deviation up to 15%)	No inhomogeneity correction
RTOG 1021/ACOSOG Z4099	3	Lung_not_GTV	%V20<=10% (minor deviation up to 15%)	Acceptable Inhomogeneity corrections specified
			D 1500 cc<=10.5 Gy	
			D_1000 cc <=11.4 Gy	

Supplemental Figure 1: Lung dose volume effect on lung toxicity. Plot shows the 2Gy-per-fraction equivalent dose (**EQD2**)

Instead of physical dose in Figure 4a for x-axis