



Pitfalls in lung stereotactic body radiotherapy – a review of organ toxicities and dose constraints

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Abstract: Stereotactic body radiotherapy (SBRT), which is also known as stereotactic ablative radiotherapy (SABR) has been established as a treatment for early-stage inoperable non-small cell lung cancer (NSCLC) in several international guidelines. One of the earliest phase I study data in lung SBRT was first published in 2003 by Timmerman and colleagues, with the same group subsequently reporting excellent phase II results. These two trials and similar landmark studies, now form the basis for lung SBRT practice internationally. Although SBRT is a standard treatment option for early stage inoperable NSCLC, it is still not available in many developing parts of the world. Because of its noninvasive nature, excellent control outcomes and safe track record. The indications for its use are expanding with more sites being treated as well as increasing use in early stage operable lung tumours and oligometastatic setting. There are still uncertainties with regards to optimal radiotherapy dose-fractionation regimen and because of the large ablative doses used in SBRT, there is a potential for significant side effects. Certain scenarios like treatment of central or recurrent tumors require greater care. In this paper, we elaborate on the common toxicities reported in literature in relation to SBRT of lung tumors as well as factors that may alter these risks.

Keywords: Stereotactic body radiotherapy (SBRT); stereotactic ablative radiotherapy (SABR); primary lung cancer; toxicities; organs at risks (OAR); dose-constraints

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Introduction

Stereotactic body radiotherapy (SBRT), which is also known as stereotactic ablative radiotherapy (SABR), has been established as a treatment for early-stage inoperable non-small cell lung cancer (NSCLC) in several international guidelines. One of the earliest phase I study data in lung SBRT was first published in 2003 by Timmerman and colleagues (1), with the same group subsequently reporting excellent phase II results (2). These two trials and similar landmark studies, now form the basis for lung SBRT practice internationally.

Although SBRT is a proven treatment option for early

stage inoperable NSCLC, it is still fairly new and not available in many developing parts of the world. There are still uncertainties with regards to optimal radiotherapy dose-fractionation regimen and because of the large ablative doses used in SBRT, there is a potential for significant side effects. In this paper, we elaborate on the common toxicities reported in literature in relation to SBRT of lung tumors as well as factors that may increase these risks.

Organs at risks (OAR)

The common toxicities reported in literature relating to

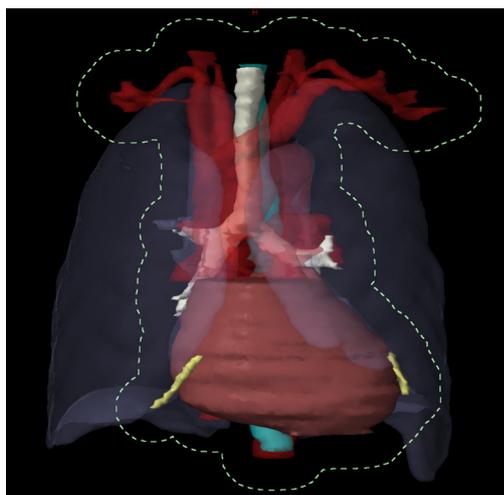


Figure 1 Central “no-fly” zone (light green dashed lines) was initially defined by Timmerman *et al.* (3) as tumor within or touching the zone 2 cm in all directions around the proximal bronchial tree. The IASLC expanded this definition to include tumors within 2 cm to any mediastinal critical structure, including the esophagus, heart, major vessels, spinal cord, brachial plexus, phrenic and recurrent laryngeal nerve (4).

SBRT of lung tumors can be divided into general radiation therapy related, like fatigue, and specific toxicities relating to structures within the thorax such as the heart, chest wall (CW), lung, major airways, greater vessels and esophagus. Collectively, these structures are known as organs at risks. This is especially important to tumors located close to these structures [e.g., centrally located tumors (*Figure 1*)] or in situations where a patient may be at greater risk of toxicities (e.g., patients with reduced lung function).

The radiobiological effects of extreme hypofractionation on tissues are not fully understood (5-7) and existing models may not provide accurate normal organ tolerances (8). It is thus not advisable to freely apply the OAR dose limits used in conventional radiotherapy on SBRT. However, due to the lack of long-term data and limited patient numbers, the linear-quadratic model is still often used for radiotherapy planning.

In 2010, with the increasing use of SBRT, the American Association of Physicist in Medicine Task Group 101 (AAPM TG101) (9) published their recommendations of OAR dose constraints (*Table 1*) in the first attempt at guiding radiotherapy planning. Notably, most of the recommended constraints were derived anecdotally and not validated. Subsequent published studies have helped refine

organ constraints further with reasonable toxicity rates reported so far.

Reported toxicities in prospective series

Many well conducted prospective trial protocols have published OAR dose limitations (*Table 1*). These serve as guidelines for many centers and allow the safe and effective delivery of SBRT techniques.

Radiotherapy related toxicities are graded by severity based on the Common Terminology Criteria for Acute Adverse Events (CTCAE) (15) or the RTOG/EORTC (16) late radiation morbidity scoring schema. However, a common problem when reporting toxicities is the interplay of other factors e.g., infection, systemic treatment toxicities or comorbidities like chronic obstructive pulmonary disease (COPD) and tumor progression that can make the direct attribution from radiotherapy alone hard to interpret. Nonetheless, grade 3 toxicities and above ($\geq G3$) are considered severe as there would be impairment of function requiring some form of intervention.

A literature review of SBRT primary lung prospective trials was performed. Nineteen trials, from 21 published articles and 5 abstracts were found, with a total of 1,381 patients reported. Data that was reported from the same center and trial were combined as the patients were assumed to be from the same cohort. The study, trial type, size, tumor criteria, radiotherapy dose-fractionation, median follow-up and reported $\geq G3$ toxicities are tabulated (*Table 2*). Reported $\geq G3$ toxicities rates ranged from 0–29.8%. There were 21 cases of grade 5 (G5) toxicities.

From *Table 2* we see that SBRT doses vary between centers. Choice of dose regimen and are often determined by physician comfort, tumor and patient characteristics. These trials along with other retrospective series have increased our appreciation for the toxicities in lung SBRT and provided the evidence for organ dose tolerances. Recognizing these potential toxicities allows us provide an informed decision and allow for safe delivery of treatment.

Toxicities by site

Lung

One of the most common toxicities related to SBRT of the lung is radiation pneumonitis (RP) (*Figure 2*), which can range from asymptomatic to symptomatic breathlessness, fevers, cough and even death from respiratory failure.

Table 1 OAR dose constraints recommended from different guidelines/trial protocols

Guideline	AAPM TG 101 (9)					RTOG 0236/0618 (2,10)		RTOG 0915 (11)		RTOG 0813 (12)		JCOG 0702 (13)		UK SABR consensus (14)						
	Vol (cc)	DC (Gy)	1#	3#	5#	Vol (cc)	DC (Gy)	3#	Vol (cc)	DC (Gy)	4#	Vol (cc)	DC (Gy)	4#	Vol (cc)	DC (Gy)	1#	3#	5#	8#
Spinal cord [†]	Max	14	21.3	30	30	Max	18	18	Max	26.0	Max	30	Max	25	Max	10 [†] /14 [*]	18 [†] /21.9 [*]	23 [†] /30 [*]	25 [†] /32 [*]	
	<0.35	10	18	23		-	-	-	<0.35	20.8	<0.25	22.5	-	-	1	7 [*]	12.3 [*]	14.5 [*]		
	<1.2	7	12.3			-	-	-	<1.2	13.6	<0.5	13.5	-	-	-	-	-	-	-	-
Brachial plexus	Max	17.5	24	30.5	Max	24	24	24	Max	27.2	Max	32	-	-	Max	-	24 [†] /26 [*]	27 [†] /29 [*]	27 [†] /38 [*]	
	<3	14	20.4	27		-	-	-	<3	23.6	<3	30	-	-	-	-	-	-	-	-
Lungs [‡]	1,500	7	11.6	12.5		V20 <10%			1,500	11.6	1,500 cc	12.5	V20<37%		-	-	-	-	-	-
	1,000	7.4	12.4	13.5		-	-	-	1,000	12.4	1,000 cc	13.5	-	-	-	-	-	-	-	-
Esophagus	Max	15.4	25.2	35	Max	27	27	27	Max	27	Max	105% PD	≤1	40	-	-	-	-	-	-
	<5	11.9	17.7	19.5		-	-	-	<5	18.8	<5	27.5	≤10	35	-	-	-	-	-	-
Heart/ pericardium	Max	22	30	38	Max	30	30	30	Max	34	Max	105% PD	-	-	Max	-	24 [†] /29 [*]	27 [†] /29 [*]	50 [†] /60 [*]	
	<15	16	24	32		-	-	-	<15	28	<15	32	-	-	-	-	-	-	-	-
Great vessels	Max	37	45	53		-	-	-	Max	49	Max	105% PD	≤1	40	Max	-	45 [*]	53 [*]		
	<10	31	39	47		-	-	-	<10	43	<10	47	≤10	35	-	-	-	-	-	-
Major Airways	Max	20.2	30	40	Max	30	30	30	Max	34.8	Max	105% PD	≤10	40	Max	-	30 [†] /32 [*]	32 [†] /35 [*]	32 [†] /44 [*]	
	<4	10.5	15	16.		-	-	-	<4	15.6	<4	18	-	-	-	-	-	-	-	-
Skin	Max	26	33	39.5	Max	24	24	24	-	-	Max	32	Max	40	Max	-	33 [*]	39.5 [*]		
	<10	23	30	26.5		-	-	-	-	-	<10	30	-	-	10	-	30 [*]	36.5 [*]		
Chest wall	-	-	-	-		-	-	-	-	-	-	-	-	-	Max	-	37 [*]	39 [*]	39 [*]	
	-	-	-	-		-	-	-	-	-	-	-	-	-	30	-	30 [*]	32 [*]	35 [*]	
Rib	Max	30	36.9	43		-	-	-	Max	40					-	-	-	-	-	-
	<1	22	28.8	25		-	-	-	<1	32					-	-	-	-	-	-
	<30	-	30			-	-	-	-	-					-	-	-	-	-	-

#, fraction; ^, optimal dose constraint; *, maximum allowed dose constraint. Vol, threshold volume; DC, dose constraints; Max, maximum point dose to organ; PD, prescribed dose; †, spinal cord planning organ at risk (PRV) is used in some guidelines (PRV = OAR + 3-5 mm expansion). ‡, lung OAR = Total Lung volume - Gross Tumour Volume (GTV); OAR, organ at risk.

Table 2 Prospective SBRT studies for primary NSCLC

Study	Trial type	Patient numbers	Criteria	Treatment dose (Gy/fraction)	Median follow-up (months)	Toxicity (graded 3 and above)	Remarks
Timmerman <i>et al.</i> 2006 (3), Fakiris <i>et al.</i> 2009 (17) (Indiana)	Ph 2	70	Inoperable, any location, T _≤ 7 cm	T1 60 Gy/3#; T2 66 Gy/3#	50.2	G3-4 AE (10%)—6 Pulmonary, 1 Anxiety. G5 AE (7.1%)—4 pulmonary, 1 hemoptysis	5/48 peripheral vs. 6/22 central G3-5 events (P=0.088); FEV1 and DLCO did not predict for RT toxicities (18); DLCO decline 1.11 mL/min/mmHg (P<0.001)
Baumann <i>et al.</i> 2009 (19)	Ph 2, multicenter European	57	Inoperable, peripheral, T _≤ 5 cm	45 Gy/3#	35	G3-4 AE (29.8%), 11 pulmonary, 3 CW, 1 fatigue, 1 heart	
Timmerman <i>et al.</i> 2010, 2014 (RTOG 0236) (2,20)	Ph 2, multicenter North American	55	Inoperable, peripheral, T _≤ 5 cm	60 Gy/3# (54 Gy/3# with density heterogeneity)	34.4	G3 AE 15/55 (27.3%), G4 AE 2/55 (3.6%), G5 AE 0	At 2 years FEV1 and DLCO declined 5.8% and 6.3% respectively. PFT and dosimetric Lung parameters did not correlated with risk of RP (21)
Ricardi <i>et al.</i> 2010 (22) (Torino)	Ph 2	62	Peripheral, T _≤ 5 cm	45 Gy/3#	28	G3 RP (3.2%). 1 rib fracture, 3 (4.8%) chronic pain syndrome	MLD main predictor of toxicity; no change in FEV, TLV, VC (23)
Le <i>et al.</i> 2006 (24) (Stanford)	Ph 1, dose escalation	32	Inoperable, any location, T _≤ 5 cm, primary/recurrent/ mets	15 Gy single fraction at 5 Gy dose increments to 30 Gy	18	G3 pulmonary 1/32 (3.1%), G5 3/32 (9.4%)	All G5 had receive chemo, 2 had prior radiotherapy; most toxicities in central tumors, G3 happened at ≥25 Gy; no change in FEV1, FVC or DLCO at 3 months
Fritz <i>et al.</i> 2006 (25) (Marburg)	Prospective	58	Inoperable, T _≤ 5 cm, primary/ mets	30 Gy/1#	22 (mets); 18 (primary)	no cases of ≥G3 AE	
Videtic <i>et al.</i> 2015 (11) (RTOG 0915)	Randomized	84	Inoperable, peripheral, T<5 cm	34 vs. 48 Gy/4#	30.2	34Gy/4# ≥G3 AE (10.3%), 1 G5 AE (not-RT related). 48 Gy/4#: ≥G3 AE (13.3%), 1 G5 AE (pulmonary)	
Nagata <i>et al.</i> 2015 (26) (JCOG 0403)	Ph 2	164	Any location, T _≤ 3 cm	48 Gy/4#	67	G3 AE (8.9%), G4 AE (1.2%); no G5	
Timmerman <i>et al.</i> 2013 (10) (RTOG 0618)	Ph 2	26	Operable, peripheral, T _≤ 5 cm	54 Gy/3#	25	G3 AE (15.4%) no G4-5	
Allibhai <i>et al.</i> 2013 (27) (PMH)	Prospective	185	Inoperable, any location, T1-2	Peripheral: T1 48 Gy/4#, T2 54-60 Gy/3#; central: 60 Gy/8# or 50 Gy/10#	15.2	G3 RP (1.8%) no G4-5 RP	RP not associated with V20 Gy or MLD

Table 2 (continued)

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Study	Trial type	Patient numbers	Criteria	Treatment dose (Gy/fraction)	Median follow-up (months)	Toxicity (graded 3 and above)	Remarks
Timmerman <i>et al.</i> 2003 (1), McGarry <i>et al.</i> 2005 (28) (Indiana)	Ph 1, dose escalation	47	Inoperable, Any location, T <7 cm	24 Gy/3# at 6 Gy/# dose increments to 72 Gy/3#	NR	G3-4 AE (14.9%)—4 pulmonary, 1 skin, 1 pericardial effusion, 1 trachea necrosis	
Shibamoto <i>et al.</i> 2012 (29,30) (Nagoya)	Prospective, multicenter Japanese	180	Inoperable, any location, T ≤5 cm	T <1.5 cm: 44 Gy/4#; T 1.5–3 cm: 49 Gy/4#; T >3 cm: 52 Gy/4#	52.5	G3 RP (1.1%) and pleural effusion (0.6%), ≥ G2 esophagitis (1.7%), rib fracture (2.2%) and dermatitis (3.9%)	
Taremi <i>et al.</i> 2012 (31) (PMH)	Prospective	108	Inoperable, any location, T1-2	Peripheral: 48 Gy/4#, 54 Gy/3#, 60 Gy/3#; central: 60 Gy/8#, 50 Gy/10#	19.1	G3 early AE (3.7%), 2 pulmonary, 1 fatigue, 1 CW. G3 late AE (5.6%)—3 CW, 3 pulmonary; no G4-5 AE	
Bezjak <i>et al.</i> 2016 (12,32) (RTOG 0813)	Ph 1/2, dose escalation	120	Inoperable, central, T <5 cm	50 Gy/5# at 0.5 Gy dose/# increments to 60 Gy/5#	26.6	≥ G3 AE (12.5%); 4 G5 AE	
Chang <i>et al.</i> 2015 (33)	Pooled analysis, 2 RCTs STARS and ROSEL	31	Operable, any location (STARS), peripheral (ROSEL), T <4 cm	STARS: peripheral 54 Gy/3#, central 50 Gy/4#; ROSEL: 54 Gy/3# or 60 Gy/5#	40.2	G3 AE (10%)—dyspnea/cough, chest wall pain, fatigue; no G4-5 AE	
Lindberg <i>et al.</i> 2017 (34) (Nordic-HILUS)	Ph 2, multicenter nordic	74	Inoperable, central, T <5 cm, mets or primary	56 Gy/8#	NR	≥G3 AE (28%); 7 G5 AE (6 hemoptysis, 1 pneumonitis)	Tumors close to main stem vs. lobar bronchus increased risk of G4-5 AE (19% vs. 3%)
Kimura <i>et al.</i> 2017 (35) (JROSG10-1)	Ph 1, multicenter Japanese, dose escalation	10	Inoperable, central, T ≤3 cm	52–60 Gy/10#	39	No cases of ≥ G3 AE	
Onimaru <i>et al.</i> 2015, 2017 (13,36) (JCOG 0702)	Ph 1, multicenter Japanese, dose escalation	28	Peripheral, T =3–5 cm, PTV <100 cc	40 Gy/4# at 5 Gy total dose increments to 60 Gy/4#	28.8	No cases of ≥ G3 AE	
Nagata <i>et al.</i> 2005 (37) (Kyoto)	Ph 1/2	45	Peripheral, T =3–5 cm, PTV ≥100 cc	40 Gy/4# at 5 Gy total dose increments to 50 Gy/4#	45.5	No cases of ≥ G3 AE	
Bral <i>et al.</i> 2011 (38) (Belgium)	Ph 2	40	Any location, T <4 cm	48 Gy/4#	30	No cases of ≥ G3 AE	
			Any location, T ≤6 cm	Peripheral: 60 Gy/3#; central: 60 Gy/4#	40	≥G3 AE (20%)—All pulmonary; no G5 AE	

Ph, phase; mets, metastatic lesion; T, tumour size/stage; AE, adverse events; #, fraction; G, grade; CW, chest wall; FEV1, forced expiratory volume in 1 second; PFT, pulmonary function test; DLCO, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; RP, radiation pneumonitis; MLD, mean lung dose; V20 Gy, volume of lung receiving 20 Gy.

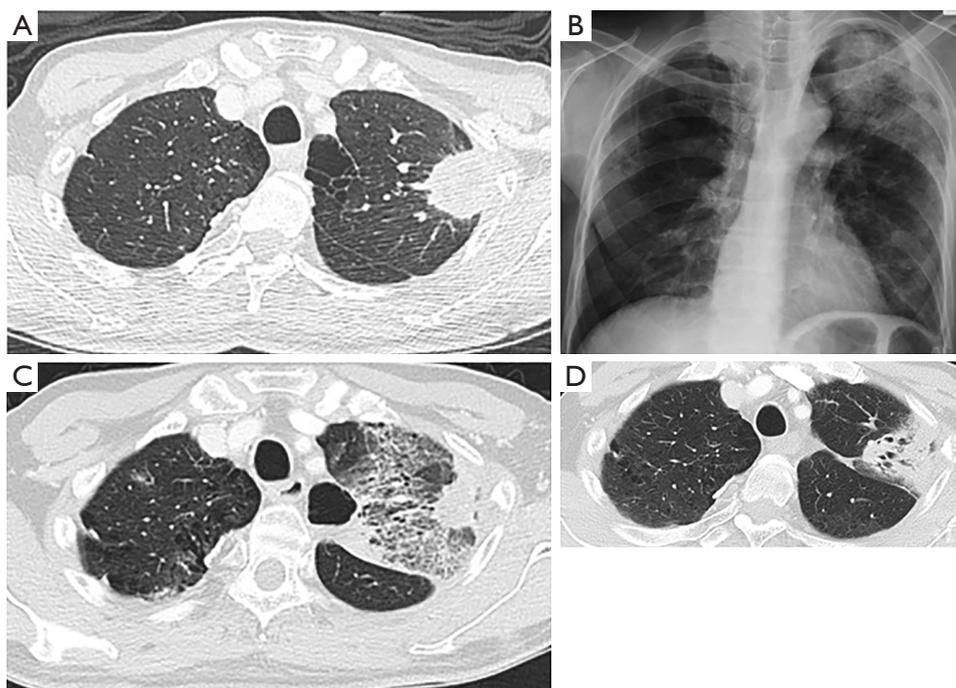


Figure 2 Case of grade 3 radiation pneumonitis (A) a 66-year-old male smoker with 3.5 cm peripheral primary lung tumor. CT scan shows bilateral emphysematous changes at the apices; (B) 6.5 months after SBRT of 48 Gy/4#. Patient had fever, cough and shortness of breath that did not improve with a course of antibiotics. Chest X-ray shows left upper and right middle zone air-space opacities; (C) CT scan shows left upper zone focal consolidation with patchy ground-glass changes in other areas in the lung. Patient was diagnosed with G3 radiation pneumonitis; (D) CT performed 2 months after treatment with steroids showed near resolution of previously noted parenchymal opacities. Scarring, volume loss and traction bronchiectasis in location of previous tumor. The V20 Gy was 4.3% (lungs-GTV) and 9.1% (ipsilateral lung). CT, computed tomography; GTV, gross tumour volume.

The non-specific presentation of RP and contributory comorbidities can make it difficult to distinguish an acute episode of radiation induced pneumonitis from other differentials like pneumonia or COPD exacerbations. This makes the comparison of incidence between studies difficult.

In a large pooled cohort study of 505 cases (39), the rate of \geq G2 and \geq G3 pneumonitis was 7% and 2% respectively. There was 1 case (0.2%) of G5 pneumonitis. Time from RT to onset of pneumonitis was a median of 0.4 years. The risk can vary with some series reporting up to 12% cases of life-threatening RP (3,40). The risk of toxicities is noted to be more in patients with central and large lesions (3,41). Mid-lower lung lesions (42-44) are also at an increased risk of RP. This may partly be attributed to greater radiosensitivity of the area, functional importance of the lower lung (45) and increased respiratory motion (44), which results in a larger planning target volume (PTV).

An association between different dosimetric parameters

and rates of RP has been noted in several studies. Barriger *et al.* reported mean lung dose (MLD) >4 Gy (4.3% *vs.* 17.6%; $P=0.02$) and a volume of lung receiving 20 Gy (V20 Gy) $>4\%$ (4.3% *vs.* 16.4%; $P=0.03$) being associated with an increased risk of G2-4 RP (46). Yamashita *et al.* and Inoue *et al.* similarly reported the predictive significance of MLD and V20 Gy (40,47). The ipsilateral MLD >9.14 Gy, total lung V5, V15, V20, V25 and V40 Gy $\geq 6.3\%$ have also been associated with higher rates of RP (48-50). Doses to the contralateral lung V5 Gy $>26\%$ and MLD >3.6 Gy have been associated with increased rates of RP as well (51,52). Another parameter looked at is the conformity index (CI) which measures the ratio of volume treated to prescribed dose over the PTV. This is ideally kept as close to 1 as possible, to ensure the high dose region conforms to the target volume. Notably, RP occurs at a significantly increased frequency in patients with poor CI ($P=0.0394$) (40).

Patient related factors such as older age, pre-existing pulmonary comorbidities and female gender are associated

with increased risk of RP (53-56). Interestingly, smoking was found to be protective against RP in some studies (54,57-60). Genetic factors such as single nucleotide polymorphisms (SNPs) of heat shock protein beta-1 (HSPB1) (61), methylene tetrahydrofolate reductase gene (MTHFR; rs1801133) (62), vascular endothelial growth factor (VEGF) gene (63), ataxia-telangiectasia mutated (ATM) (64-66) and Nijmegen breakage syndrome 1 (NBS1) genes (66) are also at increased risk of RP.

A pulmonary function test (PFT) done before SBRT does not always predict for RP (21,67). Changes in post-treatment PFT are usually minimal (18,23,24,68), although it will be decreased in the presence of RP or lung disease. The presence of baseline interstitial lung disease (48,49,69-71) and collagen vascular disease (CVD) (72) is a significant predictor of RP. In patients with idiopathic pulmonary fibrosis, the pre-treatment 18F-fluorodeoxyglucose (FDG) on positron emission tomography (PET) non-target lung uptake may serve as a biomarker for degree of baseline inflammation and predict the risk for RP (73).

Inflammatory cytokines to predict for RP has been extensively studied. Plasma transforming growth factor beta (TGF β) is a cytokine which stimulates proliferation of fibroblasts, collagen synthesis and associated pulmonary fibrosis. It is chronically elevated in patients with CVD (72). TGF β -1 polymorphisms (74) and elevated levels of TGF β -1 after radiotherapy have been associated with an increased RP risk (75,76). Other serum biomarkers such as elevated pre- & post-treatment interleukin (IL)-6 (77,78) and IL-8 (79) have been associated with higher rates of RP. Pre-treatment levels of Krebs von den Lungen (KL-6), a circulating mucin-like glycoprotein expressed and secreted from bronchial epithelial cells and type II pneumocytes, and lung surfactant protein (SP-D) are also associated with an increased risk of severe RP (80). Elevated post-treatment KL-6 levels are correlated to higher RP incidence as well (81).

To date, these markers are not routinely screened and have not been prospectively validated for clinical use. In the future, a combination of biomarkers, patient and dosimetric parameters may improve the ability to predict RP and allow for better individualization of target doses to reduce lung toxicities.

Heart

A wide spectrum of heart toxicities are noted following

conventional radiotherapy. Early toxicities include pericarditis and pericardial effusion. Late toxicities manifest 10–15 years after radiotherapy as disease of the coronary arteries, heart valves, conductive system and myocardium. Microvascular changes and accelerated coronary sclerosis are thought to contribute to the process (82). Studies on radiation effects of the heart are mostly obtained from conventionally treated breast and mediastinal lymphoma patients. Darby *et al.* showed a 7.4% increased risk of ischemic heart disease per Gy (mean heart dose) (83). An RTOG 0617 trial randomized patients between high *vs.* standard conventional dose RT for lung cancer and reported heart V5 and V30 Gy as significant predictors for worst survival (84,85).

The effects SBRT doses have on the heart are less understood. A large retrospective analysis of 803 patients treated with SBRT reported that maximum point dose (Dmax) to the left atrium of median 6.5 Gy (P=0.035) and dose to 90% of the vena cava (D90%) of median 0.59 Gy (P=0.008) were both associated with non-cancer deaths (86). Increased cardiac uptake on FDG PET after SBRT may be a marker of radiation induced myocardial injury and was noted to be associated with a cardiac V20 Gy >5 cm³ (87).

An institution in Florence treated 16 patients with paracardiac/cardiac lesions up to 36 Gy in 3 fractions at the 70% isodose line. At a median follow-up of 6.7 months, no cardiac event or echocardiography changes were noted (88). However, it is important to note that SBRT patients tend to have a better prognosis and therefore a longer time to develop late heart toxicities. It is thus advisable to keep heart doses to a minimum during radiotherapy planning.

Major vessels

Major vessels include the aorta, pulmonary vessels and superior vena cava. Radiation damage to these structures can result in hemoptysis, exsanguination secondary to rupture, aortic aneurysms or dissection and pulmonary hemorrhage.

Xue *et al.* recently published a logistic dose-response model for aorta and major vessels based on a total of 625 cases. They estimated that at Dmax =52.5 Gy in 5 fractions, the risk of grade 3–5 toxicity was 1.2%. At Dmax =45 Gy in 3 fractions, the risk was 2.3% (89). They concluded that following internationally recommended constraints, sufficiently high doses can be achieved with low risks to the vessels.

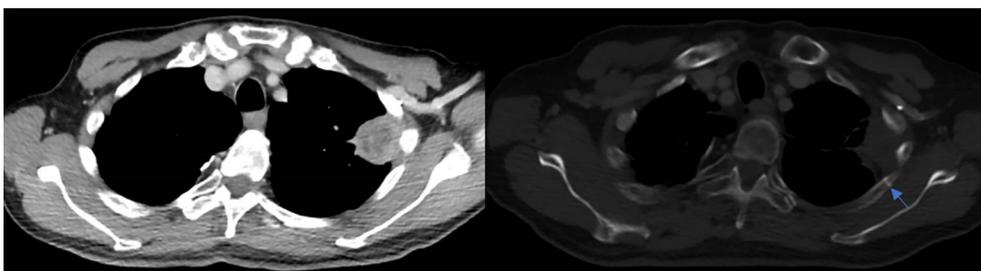


Figure 3 Asymptomatic rib fracture (blue arrow) noted 33 months after 48 Gy/4# SBRT of a peripheral tumor. The chest wall V30 Gy was 83.6 cc.

Central airways

The proximity of centrally located lesions increases the risk of central airways toxicities. This can result in atelectasis, stenosis/stricture, airway necrosis, fistula formation or even fatal hemoptysis (90). A phase II study from Indiana University reported 11-fold higher risk of G3–5 toxicities, with 4 deaths associated with central location (3). The most common severe toxicity in the trial were hemoptysis, stenosis, airway occlusion and fistula formation. At median follow-up of 50.2 months, the risk of toxicity remained higher compared to peripheral lesions (27.3% *vs.* 10.4%) (17).

At conventional high dose (≥ 73.6 Gy) RT, Kelsey reported a 6% to 57% narrowing of mainstem bronchus in 17 of 18 patients (91). The degree of stenosis was dose dependent and progressed with increasing time after radiotherapy. It was worse if the patient received chemotherapy.

With SBRT, Song *et al.* reported that at doses of 40–60 Gy in 3–4 fractions to central tumors, 8 of 9 patients (89%) showed complete or partial bronchial stricture at a median follow-up time of 26.5 months (92). Karlsson *et al.* prescribed doses of 20–50 Gy in 2–5 fractions for central tumors and reported incidence of 24.3% radiation-induced atelectasis at a median time of 8 months (1.1–30.1 months). On analysis, there was a dose dependent correlation. The median 2 Gy equivalent doses to 0.1 cm^3 of bronchial tree in patients who developed atelectasis was 210 *vs.* 105 Gy in who did not ($P=0.031$) (93).

Duijm *et al.* reported results in 134 patients treated with SBRT to central tumors. They correlated toxicities in different parts of the airway with dosimetric parameters. Higher grade toxicities such as occlusion and atelectasis were reported in the lobar and segmental bronchi. When 0.5 cc of segmental bronchi was irradiated to 50 Gy in

5 fractions, the likelihood of occlusion was 50%. For the mid- and mainstem bronchi, the 50% risk to develop grade 1 radiographically evident side effects was a Dmax of 55 and 65 Gy respectively (94).

Fatal hemoptysis attributed to high-dose RT are uncommon but have been reported in literature (95–98).

Esophagus

The esophagus is another dose limiting organ in central lung SBRT. Reported side effects range from mild esophagitis to life-threatening strictures, perforations and trachea-esophageal fistulas (1,99). Cox *et al.* reported 6.8% $\geq G3$ esophageal toxicities in 182 patients treated with 24 Gy single fraction paraspinal radiosurgery (100). The incidence increased with higher doses-volumes. At the median split $D_{2.5 \text{ cm}^3} > 14.02$ Gy, the risk was increased 6-times ($P=0.01$). They recommended a Dmax of 22 Gy.

However, despite keeping SBRT doses-volume to constraints that are considered safe (D5 cc 14.5 Gy, D2 cc 15–20 Gy, and Dmax of 19 Gy), Abelson *et al.* reported 2 incidence of high grade toxicities (esophageal fistula and esophageal perforation) in 31 patients (101). Notably, these 2 patients had received chemotherapy which is felt to be a co-factor.

In a systematic review, which included data from 563 central lung tumors from 20 studies, the incidence of G3–4 toxicities was 8.6% (102). The risk of treatment related mortality was reduced when tumor biological equivalent dose (BED) was < 210 Gy (3.6% *vs.* 1%). The authors concluded that acceptable control and limited toxicities could be achieved with appropriate fractionation regimens e.g., 50 Gy in 5, 54 Gy in 6, 56 Gy in 7 and 60 Gy in 8.

Further research is needed to establish more reliable dose limits for mediastinal structures. The RTOG 0813 (12,32), Nordic-HILUS (34) and EORTC LungTech (103)

Table 3 MD Anderson Cancer Centre (130-132) critical organ dose—volume limits for central and superior NSCLC lesions with 50 Gy in four fractions SBRT re-irradiation

Organ	Volume (cc)	Total dose/dose per fraction (Gy)
Esophagus	≤1	35/8.8
	≤10	30/7.5
Brachial plexus	Any point	<40
	≤1	35/8.8
	≤10	30/7.5
Trachea	≤1	35/8.8
	≤10	30/7.5
Main bronchus and bronchial tree	≤1	40/10
	≤10	35/8.8
Heart	≤1	40/10
	≤10	35/8.8
Whole lung (excluding GTV)	V20	<20%
	V10	<30%
	V5	<40%
Major vessels	≤1	40/10
	≤10	35/8.8
Skin (to 5 mm)	≤1	40/10
	≤10	35/8.8
Spinal cord	≤1	20/5
	≤10	15/3.8

NSCLC, non-small cell lung cancer; SBRT, stereotactic body radiotherapy; GTV, gross tumour volume.

trials are phase II SBRT trials that will provide a better understanding of treatment of central lung tumors.

CW, skin and ribs

CW pain, rib fractures (*Figure 3*) and skin toxicities are associated with peripheral lung tumors. The mechanisms for CW pain are unclear and suspected to be due to damage of soft tissue, neurovascular bundle and bone (104). The correlation between rib fractures and CW pain is less certain, with majority of CW pain presenting without rib fractures or vice versa (105,106).

Creach *et al.* reported that CW doses receiving

V30–40 Gy was most predictive of CW pain. A V30 Gy threshold of 0.7% and V40 Gy threshold of 0.19% was correlated with a 15% risk of CW pain (106). Mutter *et al.* reported similar findings in that V30 Gy >70 cm³ correlated with the presence of CW pain (104). Stephans *et al.* reported similar dose volume constraints and by maintaining V30 Gy ≤30 cm³ and V60 Gy ≤3 cm³ should result in a <10–15% risk of late CW toxicity (107).

Grills *et al.* reported in 483 patients, the incidence of rib fracture was 8% at median time of 0.9 years. This was associated with a higher BED and the optimal BED cut off was 132 Gy (11% *vs.* 5%; P=0.007) (39). Other reported parameters for dose constraints to rib or CW are Dmax =50 Gy, V40 Gy <5 cc (105) and the dose to 2 cm³ of rib (D2 cm³). At rib D2 cm³ <21 Gy/3#, the risk of the ribs fracture is close to 0%. At 27.3/3# and 49.8/3#, the risks are 5% and 50% respectively (108).

Obesity, diabetes and posterior tumors close to skin surface at an increased risk of skin and CW toxicities (109,110). Treatment factors to reduce skin toxicities should be undertaken by reducing the bolus effects from immobilization devices, calculating the skin doses and using multiple non-coplanar beams. The recommended constraints to skin reduce toxicities were reported as Dmax <50% prescribed dose (110), and reducing the volume of the CW receiving 30 Gy (V30 Gy <50 mL, 22% *vs.* ≥51 mL, 44%; P=0.02) (109).

Bonger's *et al.* compared different fractionation regimens in which 60 Gy was delivered in 3, 5 or 8 fractions depending on tumor location and did not note a significant difference between CW toxicities (111). However, in challenging cases not meeting dose constraints, longer fractionation regimens e.g., 70 Gy in 10 fractions may be a suitable alternative to reduce the risk of CW toxicities and produce similar local control rates (112).

Brachial plexus

Brachial plexus injury can happen during SBRT of apical lung tumors. Injury to the plexus can present as neuropathic pain in the shoulder or arm, motor weakness or paresthesia (113). Chang *et al.* reported that in patients with central tumors, the brachial plexopathy incidence was higher when Dmax >35 Gy and V30>0.2 cm³ (P=0.001) (114). By limiting total dose delivered to the plexus to <26 Gy in 3–4 fractions, there would be a decreased risk of brachial plexopathy at 2 years (46% *vs.* 8%, P=0.04) (115).

Thoracic re-irradiation

Recurrent lung tumours after prior radical treatment poses technical challenges due to concerns of cumulative doses. SBRT of recurrent lesion could possibly provide better control benefit and reduce the toxicities because of smaller margins and tighter dose constraints. Most of the data comes from retrospective reports and a few prospective studies of both conventional and hypofractionated regimens.

Irradiation outcomes after SBRT reirradiation have yielded variable toxicity results. Reported severe \geq grade 3 toxicity rates varied between 0% in some studies (116-122), to as high as a 10% incidence of G5 bleeding (123). Some studies noted no association between toxicities and lung dosimetric parameter, BED or overlap with prior radiotherapy fields (123-126). The risk is however increased with central tumour reirradiation.

Kilburn *et al.* (127) reported an incident (9.1%) of grade 5 aorta-esophageal fistula after reirradiation of a central tumour. The patient's aorta and esophagus had received an estimated summed EQD2 of 200 and 106 Gy (128) respectively. Trovo *et al.* (125) reported high incidences of grade 5 (1 pneumonitis and 1 hemoptysis) and grade 4 (4 pneumonitis) toxicities after 30 Gy in 5–6 fractions in 17 patients with central tumour recurrences. The heart Dmax (mean 27 *vs.* 10 Gy), D5 (minimum dose to at least 5% of the heart volume) (mean 10 *vs.* 5 Gy) and D10 (mean 7 *vs.* 3 Gy) were associated with risk of severe pneumonitis. Peulen *et al.* (123) reported 3 deaths (10.3%) from massive bleeding and 1 grade 4 toxicity (superior vena cava stenosis and gastro-tracheal fistula) in patients with central lesion (n=11) *vs.* no G4–5 toxicity in peripheral lesions (n=21). Patients with a larger initial and reirradiation CTVs and a shorter interval between initial SBRT and reirradiation were at risk of more severe toxicities. Evans *et al.* reviewed patients who had undergone retreatment radiotherapy. Two of 35 (5.7%) patients had G5 toxicities at a median follow-up of 42 months. When 1 cm³ of aorta had a composite dose of \geq 120 *vs.* <120 Gy, the rate of G5 aortic toxicity was 25% *vs.* 0% respectively (P=0.047) (129).

A team from MD Anderson have reported the largest cohort series of lung SBRT reirradiation so far. Early results after doses of 50 Gy in 4 fractions, reported grade 3 toxicities of dermatitis, CW pain and brachial plexopathy (130) which were appeared related to high doses of >35 Gy to skin and ribs and >40 Gy to brachial plexus respectively. Subsequent reports (131,132) in larger cohorts reported incidences of grade 3 esophagitis, CW ulcers and cough. The reported

severe pneumonitis rates was 20.8% (132). Analysis showed association between grade 3 pneumonitis and out-of-field relapse (131), ECOG 2-3 and FEV1 \leq 65% before SBRT, $V_{20} \geq 30\%$ of the composite plan, and an previous PTV spanning bilateral mediastinum (132). It is proposed that possible reason lesser rates of pneumonitis were noted in-field relapses was that previously irradiated areas are fibrotic and less susceptible to additional damage from RP. CW pain requiring narcotics was more common in patients with in-field relapses. The dose constraints used were reported (Table 3).

Recently Chao *et al.* (133) reported a multi-institutional prospective trial using proton therapy for lung irradiation in 57 patients recurrent NSCLC. Median reirradiation dose prescribed was 66.6 Gy with 68% having concurrent chemotherapy. Cumulative point dose constrain to the spinal cord was 75 Gy (RBE). Forty-two percent \geq grade 3 acute or late toxicities were reported at a median follow-up of 7.8 months. There were 6 possible or probable RT related grade 5 toxicities—bronchopulmonary hemorrhage, neutropenic sepsis, anorexia, pneumonitis, hypoxic respiratory failure/pleural effusion and tracheoesophageal fistula. Central region overlap (≥ 41 cm³), concurrent chemotherapy, composite mean heart dose ≥ 3.94 Gy and median esophagus dose of ≥ 12.45 Gy were associated with more toxicities.

The interpretation of results from various trials can be difficult because of heterogeneous cohorts and individually small numbers. De Bari *et al.* (128) and the MD Anderson (130-132) group have published their dose constraints recommendations. However, as there still many variables that cannot be accounted for e.g., disease free interval, previous radiation toxicities, individual characteristics, the OAR constraints in this setting remains poorly defined (134). Outcome results are promising but caution must still be exercised especially in reirradiation of centrally located tumors.

Conclusions

Published literature in lung SBRT have reported good local control rates with acceptable toxicity profiles. However, with the high doses per fraction used, there is an increased risk of normal tissue toxicity compared with conventionally fractionated radiation therapy. Care must be taken to minimize radiation exposure to normal structures. This is especially important for centrally located tumors. The available trial protocols and international consensus serve as good guidelines for SBRT dose constraints. Different dose-

regimens have been used to increase the BED delivered and reduce toxicities. Future trials will aid in our understanding of the organ dose tolerances. Studies in biomarkers and individual patient risks are underway to better tailor our SBRT treatments.

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