

Stereotactic body radiotherapy for early stage lung cancer—historical developments and future strategies

Kevin L. M. Chua¹, Iris Sin¹, Kam W. Fong^{1,2}, Melvin L. K. Chua^{1,2}, Hiroshi Onishi³

¹Division of Radiation Oncology, National Cancer Centre Singapore, Singapore, Singapore; ²Oncology Academic Program, Duke-NUS Graduate Medical School, Singapore, Singapore; ³Department of Radiology, University of Yamanashi, Yamanashi, Japan

Contributions: (I) Conception and design: KL Chua, H Onishi; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Kevin L. M. Chua. Division of Radiation Oncology, National Cancer Centre Singapore, 11 Hospital Drive, Singapore 169610, Singapore. Email: Kevin.chua.l.m@singhealth.com.sg.

Abstract: The application of radiosurgery dose escalation extra-cranially in a moving target, surrounded by critical normal tissue, presents unique dosimetric and clinical challenges. Building on a strong foundation of robust technological advancements and well-planned clinical studies, lung stereotactic body radiotherapy (SBRT) has firmly established its place in the management of early stage non-small cell lung cancer (NSCLC). Nevertheless, favourable outcomes and long-term survival still evade a substantial proportion of patients, especially for central and larger peripheral lung tumours. In this review, we will document the historical developments of lung SBRT over the past decades, highlighting key studies, which have shaped current clinical practice. At the same time, we will address some of the recent advancements in radiation technology, molecular profiling and immunotherapy, and discuss how these important developments can lead to combinatorial strategies, which we hope will form the backbone of new clinical trials and drive better cure rates.

Keywords: Stereotactic radiotherapy; lung cancer; radiosurgery; molecular biomarker; genomics

Submitted Aug 08, 2016. Accepted for publication Aug 14, 2017.

doi: 10.21037/cco.2017.08.02

View this article at: <http://dx.doi.org/10.21037/cco.2017.08.02>

Introduction

Since the mid-1980s, efforts have been made to improve outcomes in non-small cell lung cancer (NSCLC) through escalating radiotherapy doses (1). However, attempts to dose escalate through either conventional fractionation or even altered fractionation has led to either disappointing tumour control or unacceptable toxicities (2-4). In the mid-1990s, the application of “intracranial radiosurgery” extra-cranially to treat small lung tumour targets was made possible with incremental technological advancements, starting first with the use of the rigid stereotactic body frame and then becoming mainstream when improvements in image guidance enabled frameless treatments and respiratory motion management. This was subsequently followed by a series of well-planned clinical studies in the early-2000s, which demonstrated efficacy

and low rates of treatment-related toxicities (5-8). Since then, lung stereotactic body radiotherapy (SBRT) has firmly established itself as a standard treatment in early stage node negative medically inoperable NSCLC, effectively doubling biological effective dose (BED) and tumour control rates that were previously achieved with conventional radiotherapy (2). No other development in the management of NSCLC has had quite the same dramatic success. In this review, we will discuss the radiobiological principles underlying lung SBRT, technical considerations that are vital to its safe delivery, existing evidence supporting its use in various clinical settings and finally explore various strategies to optimise the therapeutic ratio in lung SBRT.

Search strategy

We searched the PubMed and MEDLINE databases for

articles published in English from 1 January 2000 to 31 Dec 2016 with the keywords “conventional fractionation”, “stereotactic body radiotherapy”, “stereotactic ablative radiotherapy”, “dose escalation”, “biological effective dose”, “radiobiology”, “early stage”, “lung cancer”, “peripheral”, “central”, “toxicities”, “complications” “pneumonitis”, “Intensity Modulated Radiotherapy”, “Volumetric Modulated Arc Therapy”, “Proton therapy”, “molecular”, “genomics”, “biomarkers”. Articles were selected based on relevance, with priority given to highly cited articles, randomised clinical trials and articles written in English. Abstracts of main medical conferences were also included if survival and toxicity end-points were reported. Articles that were published before or after the search time frame were also included if they were widely referenced and highly regarded seminal work.

Radiobiology of Lung SBRT

SBRT is characterized by precision delivery of single large doses (generally ≥ 6 Gy) either in a single fraction or in a small number of fractions to a target volume (9). Delivery of radiation dose in this manner enables sharp escalation of BED as modelled by the classic linear quadratic (LQ) model resulting in better local tumour control probability (TCP) (2,10). The application of the LQ model to very large fraction sizes has been disputed due to *in vitro* and *in vivo* data suggesting an overestimation of cell killing at large single doses compared to more fractionated regimens (11). Furthermore, large radiation doses, similar to those used in SBRT, have been demonstrated to produce additional radiobiological effects including the induction of sphingomyelinase dependent ceramide-induced tumour endothelial cell apoptosis (12,13), vascular damage leading secondarily to tumour cell killing (14) as well as enhanced anti-tumour immune responses (15). However, correlation with actual outcome data for stage I NSCLC treated with typical lung SBRT dose-fractionations demonstrates accurate radiobiological modelling with both classic LQ model as well as a modified (16), “more realistic” version of the LQ model accounting for intra- and inter-tumour heterogeneity, therefore suggesting that additional radiobiological processes do not contribute significantly to cell killing in lung SBRT (17,18). This does not however mean that these additional radiobiological processes do not exist and they could yet be exploited in combination treatment

strategies involving SBRT (19,20).

Technical considerations of lung SBRT

Precision delivery of high radiation doses to a moving tumour target in the lung requires respiratory motion control, dose construction with strict adherence to normal tissue dose constraints and treatment dose delivery with setup and target verifications (21–23).

Respiratory motion management

Management of respiratory motion is absolutely necessary both at simulation and subsequently during treatment delivery. During simulation, patients are often immobilised with a whole-body vacuum cushion with or without abdominal compression and respiration motion is mostly accounted for through the use of multiple CT scans taken at various points of the normal respiratory cycle, 4-dimensional CT (4DCT) scans, slow CT scans, a CT scan acquired at deep inspiration breath-hold or other respiratory gating strategies. 4DCT scans are widely used but may be limited by irregular breathing. While slow CT is able to produce target volumes similar to 4DCT scans, they may not accurately capture lung tumours with small respiratory movements (24,25). Deep inspiration breath hold or respiratory gating techniques minimise respiratory motion and increase normal tissue sparing from increased lung volume (26). They can be performed either involuntarily through the use of a spirometer connected to a balloon valve (Active Breathing Control, Elekta, Stockholm, Sweden) or voluntarily with visual or audio-visual biofeedback systems such as SDX (Dyn'R, Toulouse, France) or Abches (APEX Medical, Tokyo, Japan) with high reproducibility (27,28). Internal fiducials, which facilitate target verification and tumour tracking, are occasionally used but are not necessary and insertion of fiducials carries significant risks of pneumothorax in a fragile patient population (23). Accounting for inter-patient variation in respiratory motion of gross tumour volume (GTV) using individually tailored respiratory management strategies ultimately creates a patient and treatment-specific internal target volume (ITV). This represents an individualised solution, which is in sharp contrast to the early days of SBRT when patients were simulated on a single CT scan and crude population based margins were applied to account for respiratory motion. Another margin will be added to the ITV for set-up uncertainties and

slight patient movements during treatment, resulting in a planning target volume (PTV). Additional margins for microscopic disease are not added during SBRT based on the understanding that any microscopic disease extending from the tumour would be dealt with by the dose fall off or penumbra (22).

Dose distribution in SBRT

In an attempt to standardize dosimetry across institutions and clinical trials, radiation therapy oncology group (RTOG) provides a set of planning guidelines to produce compact dose distributions with heterogeneous doses within the target, and steep dose gradients outside. Planning constraints limiting “hot spots” (doses greater than 105% of prescription dose) to within the PTV and enforcing a conformity index of 1.2 make the use of multiple non-opposing, non-coplanar beams with large angles between or multiple arcs with at least 180 cumulative degrees rotation imperative. At the same time, moderate dose spillage is kept to a minimum, as determined by the PTV size. Normal tissue dose-volume constraints specific to different dose-fractionations are applied. Pencil beam algorithms, which do not correct for increased electron scattering in lower-density material tend to underestimate doses in lung tumours and are not recommended in SBRT planning (21,22).

Dose-volume constraints

The determinants of dose-limiting toxicity in SBRT are organs within the thorax such as lung, central airway, bronchi, oesophagus, heart, great vessels, spinal cord and organs outside including the brachial plexus nerves, skin, stomach, small intestines, liver, chest wall and ribs. Dose-volume constraints of these normal structures are well established in conventional radiotherapy (dose per fraction of 1.8 to 2.0 Gy) and moderately hypo-fractionated schedules (dose per fraction of 3 to 5 Gy) with lower total BED_{normal tissue} (29,30). While dose equivalence can be established using the LQ model, there is uncertainty when extreme hypo-fractionated (≥ 6 Gy) doses such as those used in SBRT are applied to small volumes, especially in serially organized tissue. Therefore, dose-volume constraints specific to different dose-fractionation schedules have been systematically defined during prospective clinical studies and correlated with observed rates of toxicities. Initially, delivering SBRT to central lung lesions was thought to be

unsafe and reliable data on dose-volume constraints for mediastinal structures was not available. This has changed with a series of phase 1 dose-finding studies in central lung SBRT. The normal tissue dose-volume constraints across single-, 3-, 4-, 5- and 8-fraction lung SBRT schedules are summarised in *Table 1* (21,31-37).

Beam delivery

While 3-dimensional conformal radiotherapy (3D-CRT) and dynamic conformal arc therapy (DCAT) offer good PTV dose distributions and adherence to normal tissue dose constraints, volumetric modulated arc therapy (VMAT) has been found to be consistently better in both regards (38,39).

The clinical significance of this dosimetric advantage is however controversial. Intriguing data from a recently published large scale retrospective analysis of 803 patients treated with SBRT across five European and North American institutions found an association between low doses to the upper regions of the heart (atria and vessels) and non-cancer deaths post SBRT. The study demonstrated that a maximum point dose to the left atrium (D_{max}) of median 6.5 Gy [EQD2₃, $\alpha/\beta_{normal\ tissue}=3$; hazard ratio (HR)=1.005, $P=0.035$] and dose to 90% of the vena cava ($D_{90\%}$) of median 0.59 Gy (EQD2₃, $\alpha/\beta_{normal\ tissue}=3$; HR=1.025, $P=0.008$) were significantly associated with non-cancer deaths (40). While the link between association and causation is unclear, it is perhaps an important reminder that most patients receiving SBRT are medically inoperable with underlying cardiac and pulmonary co-morbidities. Apparently insignificant dose spillage into surrounding normal tissue may be clinically relevant and attempts should therefore be made to keep them to a minimum.

Nevertheless, beyond its dosimetric benefits, VMAT offers a shorter treatment duration and better patient comfort and compliance compared to 3D-CRT and DCAT, making it a more attractive option for SBRT (39). With VMAT or any other forms of intensity-modulated radiotherapy (IMRT) however, one has to consider the “interplay effect” and the uncertainty it brings to actual dose delivery (25). In this regard, it is perhaps reassuring that clinical outcomes from VMAT and IMRT SBRT have been excellent (39) and with measures in place such as placing constraints on multileaf collimator (MLC) motion, limiting delivery to two arcs and treatment to more than 2 fractions, the risk of clinically significant “interplay effect” in VMAT can be safely mitigated (25,41,42).

Table 1 Normal tissue dose-volume constraints across single-, 3-, 4-, 5- and 8-fraction lung SBRT schedules

LungTech trial (EORTC 22113-08113) (31)																	
Structure	JROSG 10-1 (32) ^a			RTOG 0813 (33)		JCOG 0702 (34) ^a		RTOG 0915 (35)		RTOG 0236/0618 (36,37)		AAPM TG101 report (21)		RTOG 0915 (35)		Avoidance endpoint	
	8 fr	8 fr	5 fr	4 fr	4 fr	4 fr	4 fr	3 fr	3 fr	3 fr	1 fr						
	Vol (cc)	DC (Gy)	Vol (cc)	DC (Gy)	Vol (cc)	DC (Gy)	Vol (cc)	DC (Gy)	Vol (cc)	DC (Gy)	Vol (cc)	DC (Gy)	Vol (cc)	DC (Gy)			
Spinal cord	0.5	32	Max	33.5	Max	30.0	Max	25	Max	26.0	Max	18	Max	21.9	Max	14	Myelitis
Ipsilateral brachial plexus	0.5	38	Max	40.0	Max	22.5	Max	20.8	<0.35	20.8	<0.35	Max	<0.35	18.0	<0.35	10	Neuropathy
					Max	13.5	Max	13.6	Max	27.2	Max	24	Max	24.0	Max	17.5	
Skin	-	-	Max	40.0	Max	32	Max	-	Max	27.2	Max	24	Max	20.4	<3	14.0	Ulceration
Oesophagus	Max	40	<5	40	Max	32	Max	40 (if possible)	Max	36.0	Max	24	Max	33	Max	26	Stenosis/fistula
					Max	105% PD	Max	30	Max	33.2	Max	27	Max	25.2	Max	15.4	
Heart/pericardium	No restrictions are provided but recording of DVH data for toxicity evaluation is required.	<15	40	Max	105% PD	Max	27.5	≤10	35	<5	18.8	Max	30	Max	<5	11.9	Pericarditis
Great vessels (aorta & SVC)	-	-	-	-	Max	32	Max	49	Max	28	<15	Max	<15	24	<15	16	Aneurysm
					Max	105% PD	Max	43	Max	39	Max	37					
Great vessels (aorta)	<10	58	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Aneurysm
Great vessels (SVC)	<1	48	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Stenosis/fistula
Pulmonary artery	<1	54.5	-	-	≤1	40	-	-	-	-	-	-	-	-	-	-	Aneurysm
Pulmonary vein	<1	48	-	-	Max	32	Max	35	Max	35	Max	30	Max	30	Max	20.2	Stenosis/fistula
					Max	105% PD	Max	43	Max	39	Max	37					
Trachea/bronchus	Max	44	<10	54.5	Max	105% PD	Max	40	Max	34.8	Max	30	Max	30	Max	10.5	Stenosis/fistula

Table 1 (continued)

LungTech trial

IPBSG	PTOG	ICOG	PTOG	RTOG	ASTM TC-101	PTOG
-------	------	------	------	------	-------------	------

Structure	LungTech trial (EORTC 22113-08113) (31)		JROSG 10-1 (32) ^a		RTOG 0813 (33)		JCOG 0702 (34) ^a		RTOG 0915 (35)		AAPM TG101 report (21)		RTOG 0915 (35)		Avoidance endpoint
	8 fr		8 fr		5 fr		4 fr		4 fr		3 fr		1 fr		
	Vol (cc)	DC (Gy)	Vol (cc)	DC (Gy)	Vol (cc)	DC (Gy)	Vol (cc)	DC (Gy)	Vol (cc)	DC (Gy)	Vol (cc)	DC (Gy)	Vol (cc)	DC (Gy)	
Lung	No restrictions are provided but recording of DVH data for toxicity evaluation is required (Bil lung-PTV)	V20 <20% (Bil lung-PTV)	1,500 (critical vol)	12.5 (critical vol max dose)	V20 <37% (Bil lung-GTV)	1,500 (critical vol)	11.6 (critical vol max dose)								Basic lung function
			1,000 (critical vol)	13.5 (critical vol max dose)		1,000 (critical vol)	12.4 (critical vol max dose)								pneumonitis
Chest wall	No restrictions are provided but recording of DVH data for toxicity evaluation is required	-	-	-	-	Max (rib)	40								Pain/fracture
						<1 (rib)	32								
												</			

^a, all dose constraints in this protocol are defined with regards to the planning organ at risk volume [PRV; 3–5 mm margin around every organ at risk (OAR)]; excluding rib, chest wall, liver and spleen. Vol, volume; DC, dose constraints; SVC, superior vena cava; PD, bilateral; CTV, clinical target volume; PTV, planning target volume; GTV, gross target volume.

SBRT and clinical outcomes

Some of the earliest work in lung SBRT was accomplished by investigators in Japan and at the Indiana University. In a landmark study by Uematsu *et al.*, outcomes from 50 patients treated with SBRT to dose fractionation schedules ranging from 50 to 60 Gy in 5 to 10 fractions were published in 2001. Of note, they included 18 patients who had already received prior high dose conventional radiotherapy (40–60 Gy in 20–33 fractions) and had recurred with presumably radio-resistant disease. Despite this, 47 of 50 patients achieved long-term local control (LC). Three-year overall survival (OS) was 66% and cause-specific survival was 88% (8).

Further dose escalation to improve outcomes

Meanwhile, 47 patients at Indiana University with T1-T2 N0M0 NSCLC were recruited to a dose escalation study in which they received doses starting at 8 Gy per fraction for a total of 3 fractions delivered over 2 weeks. Doses were increased in increments of 2 Gy per fraction and despite pre-existing co-morbidities, the investigators demonstrated that the maximum tolerated dose (MTD) was not reached for T1 tumours while the MTD for T2 tumours larger than 5 cm was realised at 24 Gy per fraction. Seventy-two Gy in 3 fractions was equivalent to a BED₁₀ of 244.8 Gy, which was significantly higher than anything previously achieved through conventional fractionation without significant toxicity. Furthermore, LC was excellent with only 1 failure seen when dose per fraction was higher than 16 Gy *vs.* 9 failures at doses less than 16 Gy, alluding to a dose-response relationship (43,44).

This dose-response relationship became clear when a Japanese multi-institutional study led by Onishi *et al.* demonstrated that a minimum threshold BED₁₀ of 100 Gy, prescribed to the isocentre, was required to achieve significantly better LC leading to improved OS (5). More recently, a large scale retrospective review of SBRT outcomes for 747 patients across 65 centres in the United States suggested this dose-response survival function continues to rise beyond the threshold BED₁₀ of 100 Gy, extending past 105 Gy and potentially 110 Gy (45) while Koshy *et al.* demonstrated that for larger T2 tumours, this dose response may even continue up to a BED₁₀ as high as 150 Gy (46). However, uncertainty remains on whether these doses were defined as PTV-encompassing doses or isocentric doses. Previous studies have suggested that

isocentric doses correlate better with local TCP (17) and without knowledge of the prescription doses or dose profile, it would be difficult to draw conclusions.

To achieve further dose escalation safely, studies such as JCOG 0702 have helped guide clinical practice. In this study, the subset of peripheral T2N0M0 NSCLC (>3 cm) was specifically studied based on earlier reports demonstrating improved LC in these T2 tumours when dose was escalated from 40 to 48 Gy in 4 fractions (P=0.0015) (47). The authors concluded that for peripheral PTVs smaller than 100 cc, the MTD at the D₉₅ of the PTV could be safely increased from 40 Gy in 4 fractions over 4–8 days (BED₁₀=80 Gy) to 55 Gy in 4 fractions (BED₁₀=130.6 Gy) (34). Larger tumours with PTV greater than 100 cc can be safely escalated to 50 Gy in 4 fractions (BED₁₀=112.5 Gy) (48).

Central lung SBRT

However, MTDs for peripherally located lesions cannot be applied to central lung tumours. Different definitions exist but in general, central lesions are distinguished as any tumour within or touching the zone of the proximal bronchial tree, defined as a volume of 2 cm in all directions around the proximal bronchial tree (carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus, right and left lower lobe bronchi) as well as lesions which are immediately adjacent to the mediastinal or pericardial pleura, with a PTV expected to touch or include the pleura (6,31,49). When Timmerman *et al.* at the University of Indiana carried out a single-arm phase 2 study from 2002 and 2004, it quickly became obvious that SBRT to these central lung lesions resulted in higher rates of severe toxicities with 2-year freedom from severe toxicity rates of 54% (central) *vs.* 83% (peripheral) (P=0.004) (6) and they were subsequently excluded from the RTOG 0236 study. Other reports of severe and fatal toxicities after central lung SBRT followed (50,51). The clinical need to determine the MTDs for central lesions and establish reliable dose-volume constraints for each of the mediastinal structures resulted in investigators embarking on a series of dose-finding studies.

Dose finding studies in central lung SBRT

The EORTC sponsored LungTech trial (EORTC 22113-08113) led by Nestle *et al.* opened in late 2014. In this study, central tumours were treated with 60 Gy in 8

fractions and results are awaited (31). JROSG10-1 treated only T1 NSCLC patients and found the MTD to be 60 Gy in 8 fractions. At this dose, no grade 3 or worse adverse effect within 12 months of treatment was seen and all dose constraints could be met (32). RTOG 0813 led by Bezjak *et al.* reported their MTD to be 60 Gy in 5 fractions (1 fraction every 2 days). Thirty-three patients were treated with 60 Gy in 5 fractions with a median follow-up of 29.8 months and 38 patients were treated with 57.5 Gy in 5 fractions with a median follow-up of 33 months. Two-year LC and OS rate was upwards of 87% and 70.2% respectively. While overall rate of grade 3 or greater toxicities for all 71 patients was acceptable, the authors did report 2 (5.3%) grade 5 toxicities in the 11.5-Gy cohort and 1 (3%) grade 4 oesophageal perforation and 1 (3%) grade 5 pulmonary haemorrhage in the 12-Gy cohort (33). While these risks are low, they are severe and have to be discussed with patients. Longer fractionations appear to have a better safety profile and if efficacious, could represent a risk-adapted alternative for high-risk patients for whom severe toxicities may be catastrophic.

Single-fraction lung SBRT

The ideal dose fractionation has also been a subject of study in peripheral lung SBRT. A series of studies have looked at dose escalation in a single fraction and while many of them involve heterogeneous populations including both early stage NSCLC as well as pulmonary metastases from a variety of histologies, much can be learnt about tolerability as well as dose-response.

One of the earliest studies involving single-fraction SBRT led by Wulf *et al.* used 26 Gy in a single fraction to treat 1 early stage NSCLC and 25 small lung metastases including NSCLC metastases. Despite the heterogeneous disease treated, no local failures were seen with single-fraction 26 Gy at 11 months. More importantly, no severe acute or late normal tissue toxicity was observed (52).

Hof *et al.* treated patients with doses ranging from single-fraction 19 to 30 Gy at isocentre and found improved LC with doses equivalent to or higher than 26 Gy ($P=0.032$) (53). Again, no clinically significant treatment related toxicity was observed.

Meanwhile, Hara *et al.* treated 59 patients (11 early stage NSCLC and 48 metastases) using doses ranging from 26 Gy to more than 30 Gy (range, 30–34 Gy) and observed minimal toxicity with only 1 patient (1.7%) suffering grade 3 respiratory symptoms. Doses of 30 Gy and higher seemed

to improve 2-year local progression free survival from 52% (<30 Gy) to 83% ($P=0.07$). However, the majority (88.1%) of tumours treated were smaller than 3 cm and maximum tumour size for all tumours was smaller than 4 cm (54). Studies have shown that larger treatment volumes greater than 50 cc (equivalent to a diameter greater than 4.5 cm) and patients who have received prior thoracic radiation are at significant risks of pulmonary toxicity even at single-fraction 25 Gy and higher doses should be used with caution (55).

RTOG 0915—fractionated vs. single-fraction SBRT

Comparing a single-fraction 34 Gy with the more commonly used 48 Gy in 4 consecutive daily fractions, RTOG 0915 aimed to ascertain the ideal lung SBRT dose fractionation. The primary end point of this study was rate of grade 3 or greater adverse events at 1 year and in this regard, single-fraction SBRT was found to be better tolerated {4 of 39 (34 Gy/1 fr) [10.3%, 95% confidence interval (CI), 2.9–24.2%] vs. 6 of 45 (48 Gy/4 fr) (13.3%, 95% CI, 5.1–26.8%)} while offering similar primary tumour control [2-year cumulative primary tumour failure rate 2.6% (34 Gy/1 fr) vs. 2.2% (48 Gy/4 fr)]. However, toxicities occurring at a later time point such as brachial plexopathies and longer-term decline in pulmonary function were not reported and could be clinically relevant. It is also important to note that while tumours less than 5 cm were eligible for the study, the median tumour diameter in the recruited single-fraction cohort was 2 cm (range, 1.00–4.98 cm) and it is possible that a higher toxicity rate may be seen if larger tumours had been treated (35).

Another concern with RTOG 0915 was that OS data beyond 1 year suggested a trend favouring 48 Gy/4 fr. This is despite the BED_{tumour} for single-fraction 34 Gy ($BED_{10}=149.6$ Gy) being 44 Gy higher than the BED_{tumour} for 48 Gy/4 fr ($BED_{10}=105.6$ Gy) (35). Even though this study was not powered to address differences in OS between the 2 treatment arms, advocates for fractionated SBRT have pointed to this to highlight concerns regarding tumour hypoxia-conferred radio-resistance, an effect thought to be more pronounced when treatment is delivered in a single fraction, therefore losing the protection that re-oxygenation offers fractionated treatments (20). Furthermore, single-fraction 34 Gy results in a much higher $BED_{normal\ tissue}$ ($\alpha/\beta_{normal\ tissue}=3$) of 419.3 Gy compared to a $BED_{normal\ tissue}$ of 240 Gy for 48 Gy/4 fr and previous meta-analysis had found a detrimental effect on OS when BED_{10} exceeds 146 Gy (56),

possibly due to higher dose to normal tissue resulting in increased risk of occult toxicities and non-cancer related deaths (40,57).

For these reasons, at present, fractionated lung SBRT is more widely practised. *Table 2* (35,36,52–55,58–64) summarizes a series of widely referenced lung SBRT studies involving both fractionated and single-fraction regimens.

Surgery vs. SBRT

The earliest reports from Japan included a significant proportion of patients who were medically operable but refused surgery. For example, of the 257 patients reported by Onishi *et al.*, 99 (38.5%) were medically operable. Five-year OS for these medically operable patients who received a minimum threshold BED₁₀ of 100 Gy was 72.3% (95% CI, 59.1–85.6%) for stage IA and 65.9% (95% CI, 43.0–88.9%) for stage IB (5). This was consistent with other studies, summarised in *Table 3* (5,7,8,37,65–71), which reported excellent LC and 3-year OS rates upwards of 66%. This raised the question of whether SBRT should be offered as a reasonable alternative to medically operable patients. In particular, elderly patients with small peripheral lesions and borderline lung function or medical comorbidities, for which surgery and general anaesthesia are not without risks, are thought to benefit most from non-invasive SBRT. A Dutch population-based matched-pair comparison study between SBRT and surgery for the elderly cohort found 30-day mortality to be 8.3% after surgery *vs.* 1.7% after SBRT while 3-year survival rates between the two modalities were similar at 60% for surgery *vs.* 42% for SBRT ($P=0.22$) (72). Across all studies, SBRT for medically operable patients was expectedly well tolerated with incidence rates of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or greater toxicity of up to 15% and a cumulative incidence of treatment related mortality of only 0.7% (68–71). On the other hand, overall complication rates from video-assisted and open thoracotomy lobectomy can be as high as 16.4% and 31.2% respectively (73) with 30-day post lobectomy mortality rates of about 2.4% (74).

Three separate randomised studies [ACOSOG Z4099 (NCT01336894), STARS (NCT00840749) and ROSEL (NCT00687986)] attempted to compare surgery with mediastinal lymph node sampling *vs.* SBRT delivering a minimum BED₁₀ of 100 Gy but all suffered from poor accrual and closed prematurely. A total of 58 individual patient data from STARS and ROSEL trials were

subsequently pooled and analyzed by Chang *et al.* Estimated OS at 3 years was 95% in the SABR group compared with 79% in the surgery group (log-rank $P=0.037$). The 3-year pooled estimated LC, regional control (RC) and distant control (DC) for the SBRT cohort *vs.* surgery cohort were similar at 96% *vs.* 100%, 90% *vs.* 96%, and 97% *vs.* 91%, respectively (75). SBRT appeared to be better tolerated than surgery with fewer grade 3 and greater toxicities (10% *vs.* 44%) and no treatment related deaths (0% *vs.* 4%). The authors concluded that for medically operable patients, SBRT showed at least clinical equipoise when compared to surgery. Furthermore, patient reported quality of life outcomes with SBRT have been found to be at least equal if not better than surgery (76,77).

On the other hand, with surgery and mediastinal lymph node sampling, up to 35% of patients can be upstaged, with half of these upstagings bringing about the addition of adjuvant chemotherapy (78). However, multiple studies have shown similar rates of regional and distant recurrences (62,72,75,79) for SBRT compared to surgery, perhaps due to sterilization of micrometastases through incidental mediastinal, hilar dose or the triggering of a systemic immune response against micrometastases (80). Furthermore, endobronchial lymph node sampling might be able to reduce some of the false negatives with PET-CT, which can be as high as 33.3% in higher risk central T2 lesions with a solid appearance on imaging (81,82). Isolated recurrences if they do occur can also be salvaged with definitive radiotherapy or in a few occasions salvage surgery (83–87). All in all, an argument could be made that for patients at a higher risk from surgery, SBRT should at least be discussed as an alternative.

Optimizing SBRT therapeutic ratio

Complications are rare in SBRT but relatively large hypofractionated doses mean that they can be potentially life threatening (33,58,88). These include central airway toxicities such as bronchial stenosis resulting in atelectasis (89), bronchial necrosis or hemoptysis (51), esophageal toxicities such as strictures, perforation or trachea-oesophageal fistulas (90), aortic toxicities such as hemoptysis secondary to aortic damage or aortic rupture, aortic aneurysm or aortic dissection (91), severe skin toxicities (92), chest wall pain including rib fractures (93–95), symptomatic radiation pneumonitis (RP) (96,97), and brachial plexopathies (98). Rarer complications include vagal nerve injury (99) and

Table 2 Data from the use of lung SBRT in medically inoperable patients

Study	Sample size	Patient characteristics [patient number]	PD [patient number]	Prescription point	LC/LPFS	OS	CSS	RR/RFS	DMR/DMFS	Toxicities	Others
Fractionated studies											
Fakiris <i>et al.</i> 2009 (58)	70	T1 [34]; T2 ≤7 cm [36]	T1: 60 Gy/3 fr; T2: 66 Gy/3 fr; TTD: NR	80% IDL covering >95% PTV	3 years, 88.1% (LC)	3 years, 42.7% (CI, 31.1–54.3%)	3 years, 81.7% (CI, 70.0–93.4%)	6/70 (8.6%) (RR)	9/70 (12.9%) (DMR)	G3–4 pulmonary, 7/70 (10%); G5 pulmonary, 5/70 (7.1%); G3 skin, 1/70 (1.4%); G3–5 AE, 5/48 (peripheral) vs. 6/22 (central) (P=0.088)	Phase 2
Baumann <i>et al.</i> 2009 (59)	57	T1 [40]; T2 [17]	45 Gy/3 fr EOD; TTD: 4–15 days	67% IDL	3 years, 92% (LC)	3 years, 60%	3 years, 88%	3/57 (5.2%) (RR)	3 years, 24% (DMR)	G3–4 pulmonary, 17/57 (29.8%)	Phase 2
Timmerman <i>et al.</i> 2010/2014 (36,60)	55	T1 [44]; T2 [11]	60 Gy/3 fr, 54 Gy/3 fr (after accounting for density heterogeneity); TTD: 1.5–2.0 weeks	PD covering >95% PTV (CI, 84.3–99.7%) (LC); PT + involved lobe, 3 years, 90.6% (CI, 76.0–96.5%) (LC)	PT only, 3 years, 97.6% (CI, 41.6–67.9%)	3 years, 55.8% (CI, 41.6–67.9%)	NR	Local (PT & involved lobe) + regional, 3 years, 12.8% (CI, 5.3–29.0%) (RR)	3 years, 22.1% (CI 12.3–37.8%) (DMR)	G3 AE, 15/55 (27.3%); G4 AE, 2/55 (3.6%); G5 AE, 0/55	Phase 2
Videtic <i>et al.</i> 2010 (61)	26	T1/T2 [28]	50 Gy/5 fr; TTD: 5 days	PD covering >95% PTV	3 years, 94.4% (LC)	3 years, 52%	NR	Nodal + distant, 10/28 (35.7%) (RR/DMR); distant only, 2/28 (7.1%) (DMR)	3 years, 5 years, 31% (DMR)	G3 pulmonary, 1/26 (3.8%)	Retrospective analysis of IMRT-SBRT
Cassidy <i>et al.</i> 2017 (62)	58	T1 [39]; T2 [12]; T3 [7]	Median 5 (3–8) fr x median 10 (7–20) Gy; TTD: NR	–	2 years, 84.5% (CI, 65.3–93.5%) (LC)	2 years, 56.4% (CI, 37.6–71.6%)	2 years, 72.6% (CI, 52.1–85.4%)	2 years, 28.3% (CI, 16.5–45.9%) (RR)	2 years, 14.9% (CI, 6.6–31.5%) (DMR)	G3 pulmonary, 2/58 (3.5%); G3 chest wall pain, 2/58 (3.5%); G3 oesophagitis, 1/58 (1.7%)	Retrospective analysis of patients ≥80 years

Table 2 (continued)

Table 2 (continued)

Study	Sample size	Patient characteristics [patient number]	PD [patient number]	Prescription point	LC/LPFS	OS	CSS	RR/RFS	DMR/DMFS	Toxicities	Others
Ricardi et al. 2010 (63)	62	T1 [43]; T2 [19]	45 Gy/3 fr EOD; TTD: 1 week	80% IDL	3 years, 87.8% (LC)	3 years, 57.1%	3 years, 72.5%	Local + nodal, 1/62 (1.6%) (RR); isolated nodal, 4/62 (6.5%) (RR)	15/62 (24.2%) (DMR)	≥ G3 pulmonary, 2/62 (3.2%)	Phase 2
Single fraction											
Wulf et al. 2004 (52)	61	T1 [2]; T2 [10]; T3 [8]; lung mets [51, including 23 NSCLC]	30 Gy/3 fr [19]; 36 Gy/3 fr [9]; 37.5 Gy/3 fr [17]; TTD: 7–9 days; 26 Gy/1 fr [26]	3fr: PD to 100%; 1fr: 80% IDL	T1–3 NSCLC: ≥1 year, 92% (LC)	T1–3 NSCLC: 3 years, 32%; 5 years, 18%	NR	NR	T1–3 NSCLC: ≥2 years, 25% (DMFS)	No ≥ G3 AE reported	Retrospective
Hof et al. 2007 (53)	42	T1 [17]; T2 [21]; T3 [4]	19 Gy/1 fr [1]; 22 Gy/1 fr [2]; 24 Gy/1 fr [7]; 26 Gy/1 fr [14]; 28 Gy/1 fr [10]; 30 Gy/1 fr [8]	PD to isocentre	3 years, 67.9% (LC); ≥2 years, 72% (≥26 Gy) vs. 50% (<26 Gy) (P=0.032) (LC)	3 years, 37.4%	NR	2/42 (4.8%) (RR)	13/42 (31.0%) (DMR)	No ≥ G3 AE reported	First 10 patients recruited as part of phase 1/2 trial
Hara et al. 2006 (54)	47	T1/T2 [4]; LA NSCLC [7]; Lung mets [48, including 11 NSCLC]	20–34 Gy/1 fr	NR	2 years, 78% across all patients (LPFS); 2 years, 83% (≥30Gy) vs. 52% (<30Gy) (LPFS)	2 years, 41% across all patients	NR	NR	NR	G3 pulmonary, 1/47 (2.1%)	Retrospective
Le et al. 2006 (55)	32	T1–2 [20]; recurrent/lung mets [12]	15 Gy/1 fr [9]; 20 Gy/1 fr [1]; 25 Gy/1 fr [20]; 30 Gy/1 fr [2, previously unirradiated and vol <50 cc]	PD covering >95% PTV	T1–2 NSCLC: 1 year, 78% (LC); 91% (>20 Gy) vs. 51% (<20 Gy) (P=0.03) (LC)	T1–2 NSCLC: 1 year, 85%	NR	Nodal and/or distant, 9/20 (45%) (RR/DMR)	DMR/DMR	G3 late pulmonary, 1/32 (3.1%); G5 late pulmonary, 3/32 (9.4%), all 3 patients received chemo before or after SBRT	Phase 1 dose escalation study
Fritz et al. 2006 (64)	58	T1–2 [33]; pulmonary mets [31, including 10 NSCLC]	30 Gy/1 fr	PD to isocentre; PD covering ≥80% PTV	T1–2 NSCLC: 4 years, 83% (LC)	T1–2 NSCLC: 4 years, 39%	NR	NR	NR	No ≥ G3 AE reported	Prospective

Table 2 (continued)

Table 2 (continued)

Study	Sample size	Patient characteristics [patient number]	PD [patient number]	Prescription point	LC/LPFS	OS	CSS	RR/RFS	DMR/DMFS	Toxicities	Others
Randomised											
Videtic <i>et al.</i> 2015 (35)	84	34 Gy/1 fr: {T1 [32], T2 [7]} vs. 48 Gy/4 fr: {T1 [40], T2 [5]}	34 Gy/1 fr [39] vs. 48 Gy/4 fr [45]; TTD: 4 days	≥60%, <90% IDL; PD covering >95% PTV	1 year, 97% (CI, 84.2–99.9%) vs. 1 year, 92.7% (CI, 80.1–98.5%) (LC)	2 years, 61.3% (CI, 44.2–74.6%) vs. 2 years, 77.7% (CI, 62.5–87.3%)	NR	NR	NR	34 Gy/1 fr: 1 year ≥ G3 AE, 10.3% (CI, 2.9–24.2%) [G3 pulmonary, 4/39 (10.3%)] vs. 48 Gy/4 fr: 1 year ≥ G3 AE, 13.3% (CI, 5.1–26.8%) [G3 pulmonary, 5/45 (11.1%); G5 pulmonary, 1/45 (2.2%)]	Randomised. primary endpoint 1 year ≥ G3 AE

All confidence intervals are at 95% unless stated otherwise. SBRT, stereotactic body radiotherapy; PD, prescription dose; LC, local control; LPFS, local progression free survival; OS, overall survival; CSS, cancer specific survival; RR, regional recurrence; RFS, regional-recurrence free survival; DMR, distant metastases recurrence; DMFS, distant metastases free survival; fr, fractions; TTD, total treatment duration; NR, not reported; IDL, isodose line; PTV, planning target volume; CI, confidence interval; G, grade; AE, adverse events; EOD, every other day; PT, primary tumour; IMRT, intensity modulated radiotherapy; mets, metastasis; LA, locally-advanced.

spontaneous pneumothorax (100). A post-treatment decline in pulmonary function can also be observed but it is usually not clinically significant (101).

Dosimetric parameters associated with these toxicities have been demonstrated (88–92,94,95,98,102) and have led to the establishment of dose volume constraints as previously shown in *Table 1* (21,31–37). These constraints can be achieved through more precise delivery of radiotherapy with motion management strategies, intensity modulation and non-coplanar beam deliveries (38,39) backed by meticulous quality assurance. More fractionated regimens can also be used if there is a need for gentler doses to the normal tissue. This way, one can effectively kill two birds with one stone, achieving the minimum BED_{tumour} of 100 Gy for optimal local control and cure while reducing the toxicities of treatment by utilizing the benefits of fractionation.

However, dosimetric parameters alone do not adequately account for inter-patient variation in baseline normal tissue characteristics and intrinsic radiosensitivity. To account for these individual differences, considerations based on pre-treatment clinical, normal tissue and radiological characteristics need to be made. Pulmonary function tests are often performed prior to SBRT but appear to correlate poorly with grade ≥ 2 RP and patients with poor pulmonary function achieve cause specific survival and toxicity outcomes similar to patients with better function (103). Some institutions have sought to use baseline radiological characteristics as a means to identify patients at greater risk of RP. Subclinical interstitial lung disease manifesting as honeycombing on pre-treatment CT had been found to be associated with fatal interstitial pneumonitis post-surgery (104) and similar correlations with poor outcomes have been established in high-dose radiotherapy (66,105). Combining dosimetric parameters, age and extent of pulmonary fibrosis as determined according to the modified criteria of Kazerooni *et al.* (106) in a retrospective review of 122 patients, Tsujino *et al.* from Hyogo Cancer Centre proposed a predictive score which was able to predict the incidence of grade ≥ 3 RP with an area under the curve (AUC) of 0.888 (107). However, this cohort of patients received high dose conventional radiation concurrent with chemotherapy. The use of concurrent radiation sensitizers and likely larger treatment volumes mean that their findings may have limited applicability to SBRT treatments. Furthermore, while age is a predictive factor in this study, other studies have consistently shown that elderly patients tolerate SBRT treatments just as well as younger patients (62,72). For instance, Winship Cancer Institute of

Table 3 Data from the use of lung SBRT in both medically inoperable and operable patients

Study	Sample size	Patient characteristics [patient number]	PD [patient number]	Prescription point	LC/LPFS	OS	CSS	RR/RFS	DMR/DMFS	Toxicities	Others
Medically inoperable and operable mixed cohort											
Onishi et al. 2007 (5)	257	T1 [164], T2 [93]; inoperable [158], operable [99]; BED ≥ 100 Gy [215], BED <100 Gy [42]	30–84 Gy/1–14 fr; TTD: <25 days	PD to isocentre	BED ≥ 100 Gy: 5 year, 84.2% (CI, 77.7–90.8%) vs. BED <100 Gy: 5 years, 36.5% (CI, 10.4–62.6%) (P<0.001) (LC)	3 years, 56.8% (CI, 50.2–63.5%); 5 years, 47.2% (CI, 38.7–53.5%); inoperable: 5 years, 35.0% (CI, 25.9–44.1%) vs. operable: 5 years, 64.8% (CI, 53.6–75.9%) (P<0.001)	NR	29/257 (11.3%) (RR)	51/257 (19.8%) (DMR)	G3 pulmonary, 14/257 (5.4%); G3 oesophagitis, 2/257 (0.8%); G3/4 dermatitis, 3/257 (1.2%); rib fracture adjacent to tumour 4/257 (1.6%)	Retrospective
						BED ≥ 100 Gy: 5 years, 53.9% (CI, 46.0–61.8%) vs. BED <100 Gy: 5 years, 19.7% (CI, 5.9–33.4%) (P<0.05)		BED ≥ 100 Gy: 20/215 (9.3%) vs. BED <100 Gy: 9/42 (21.4%) (P<0.05) (RR)	BED ≥ 100 Gy: 40/215 (18.6%) vs. BED <100 Gy: 11/42 (26.2%) (P=0.3) (DMR)		
						Operable & BED ≥ 100 Gy: 5 years, 70.8% (CI, 59.3–82.2%); T1: 5 years, 72.3% (CI, 59.1–85.6%); T2: 5 years, 65.9% (CI, 43.0–88.9%)					

Table 3 (continued)

Table 3 (continued)

Study	Sample size	Patient characteristics [patient number]	PD [patient number]	Prescription point	LC/LPFS	OS	CSS	RR/RFS	DMR/DMFS	Toxicities	Others
Uematsu et al. 2001 (8)	50	T1 [24], T2 [26]; inoperable [21], operable [29]	50–60 Gy/5–10 fr; TTD: 1–2 weeks Dose reduction 30–45 Gy/5–10 fr in 18 patients who also received conventional RT 40–60 Gy/20–33 fr	80% IDL	47/50 (94%) (LC)	3 years, 66%; operable: 3 years, 86%	3 years, 88%	No isolated nodal failures	7/50 (14%) (DMR)	Vertebral compression fracture, 1/50 (2%); rib fracture, 1/50 (2%)	Retrospective
Nagata et al. 2005 (7)	45	T1 [32]; inoperable 16, operable 16 T2 <4 cm [13]; inoperable 11, operable 2]	48 Gy/4 fr; TTD: 5–13 days	PD to isocentre	T1: 5 years, 95% (LPFS) T2: 5 years, 100% (LPFS)	T1: 3 years, 83%; 5 years, 83% T2: 3 years, 72%; 5 years, 72%	NR	T1: 3/32 (9.4%) (RR) T2: 0/13 (RR)	T1: 5/32 (15.6%) (DMR) T2: 4/13 (30.8%) (DMR)	No ≥ G3 AE reported.	Retrospective
Koto et al. 2007 (65)	31	T1 [19], T2 [12]; inoperable [20], operable [11]	45 Gy/3 fr [20]; TTD: 1 week 60 Gy/8 fr if near OARs [11]; TTD: 2 weeks	PD to isocentre	T1: 3 years, 77.9% (LC); T2: 3 years, 40.0% (LC)	3 years, 71.7%	3 years, 83.5%	Local + nodal, 2/31 (6.5%) (RR)	Local + distant, 1/31 (3.2%) (DMR); isolated distant, 5/31 (16.1%) (DMR)	G3 pulmonary, 2/31 (6.5%)	Retrospective

Table 3 (continued)

Table 3 (continued)

Study	Sample size	Patient characteristics [patient number]	PD [patient number]	Prescription point	LC/LPFS	OS	CSS	RR/RFS	DMR/DMFS	Toxicities	Others
Onishi et al. 2013 (66)	2,226	T1 [1601], T2 [625]; inoperable [1,500], operable [726]; BED $\geq$ 100 Gy [2,042], BED <100 Gy [184]	32–70 Gy/3–12 fr	Majority PD to isocentre	T1: 3 years, 87% (LPFS); T2: 3 years, 72% (LPFS)	3 years, 72% BED $\geq$ 100 Gy: 3 years, 75% vs. BED <100 Gy: 3 years, 63% (P<0.01)	3 years, 85%	11.3% (RR)	22.3% (DMR)	$\geq$ G3 pulmonary, 2.9%	Retrospective review across 20 institutions of JRS-SBRTSG
						Inoperable: 3 years, 68% vs. operable: 3 years, 78% (P<0.01)					
						Chronic pulmonary interstitial changes (3 years, 41%) and emphysema (3 years, 64%) did worse.					
Nagata et al. 2015 (67)	169 (164 eligible)	T1 [164]; inoperable [100], operable [64]	48 Gy/4 fr; TTD: 4–8 days	PD to isocentre	Inoperable: 3 years, 52.8% (CI, 42.6–62.1%) vs. operable: 3 years, 68.6% (CI, 55.7–78.5%) (LPFS)	Inoperable: 5 years, 42.8% (CI, 33.0–52.3%) vs. operable: 5 years, 54.0% (CI, 41.0–65.4%)	NR	All nodal, 24/164 (14.6%) (RR); local + nodal, 2/164 (1.2%) (RR); isolated nodal, 5/164 (3.0%) (RR)	44/164 (26.8%) (DMR)	G3 AE, 15/169 (8.9%); G4 AE, 2/169 (1.2%); G5 AE, 0/169	Prospective phase 2 for both inoperable and operable T1N0M0 NSCLC
						Inoperable: 3 years, 87.3% vs. operable: 3 years, 85.4% (LC)					Only eligible patients analysed for survival outcomes

Table 3 (continued)

Table 3 (continued)

Study	Sample size	Patient characteristics [patient number]	PD [patient number]	Prescription point	LC/LPFS	OS	CSS	RR/RFS	DMR/DMFS	Toxicities	Others
Medically operable only											
Onishi <i>et al.</i> 2011 (68)	87	T1 [64], T2 [23]	45.0–72.5 Gy/3–10 fr; 75 Gy/10 fr [42]; 48 Gy/4 fr [38]; TTD: most fractions on consecutive days but some were EOD.	PD to isocentre	5 years, 86.7% (CI, 78.3–94.9%) (LPFS) T1: 92.0% (CI, 83.8–99.6%) (LPFS); T2: 73.0% (CI, 52.2–93.7%) (P=0.01) (LPFS)	5 years, 69.5% (CI, 58.8–80.1%)	5 years, 76.1% (CI, 65.9–86.3%)	5 years, 85.3% (CI, 77.6–93.0%) (RFS)	5 years, 75.1% (CI, 64.8–85.4%) (DMFS)	G3 pulmonary, 1/87 (1.1%); G3 dermatitis, 3/87 (3.4%); G3 oesophagitis, 1/87 (1.1%); rib fractures, 4/87 (4.6%)	Retrospective
Eriguchi <i>et al.</i> 2017 (69)	88	T1 [63], T2 [25]	60 Gy/5 fr [16]; 50 Gy/5 fr [63]; 40 Gy/5 fr [9]; TTD: NR	PD to 80% IDL	PT only, 3 years, 96% (LC); PT + involved lobe, 3 years, 90% (LC) PT only, 5 years, 93% (LC); PT + involved lobe, 5 years, 85% (LC)	3 years, 86%; 5 years, 69%	3 years, 93%; 5 years, 88%	3 years, 5% (RR); 5 years, 8% (RR)	3 years, 87% (DMFS); 5 years, 82% (DMFS)	G3 pulmonary, 1/88 (1.1%)	Retrospective

From July 2011, PD was increased due to suboptimal LC—60 Gy/5 fr to peripheral lesions not adjacent to chest wall & 50 Gy/5 fr to peripheral lesions adjacent to the chest wall and central lesions without main bronchus or main pulmonary artery within the PTV

Table 3 (continued)

Table 3 (continued)

Study	Sample size	Patient characteristics [patient number]	PD [patient number]	Prescription point	LC/LPFS	OS	CSS	RR/RFS	DMR/DMFS	Toxicities	Others
Onishi et al. 2015 (70)	661	T1 [506], T2 [155]	32–70 Gy/4–15 fr; TTD: NR	PD to isocentre	T1: 3 years, 89% (LPFS); T2: 3 years, 80% (LPFS)	3 years, 79% BED $\geq$ 100 Gy: 3 years, 80% vs. BED <100 Gy: 3 years, 70% (P value NR) Patients with pulmonary interstitial changes (3 years, 42%) did worse.	3 years, 89%	NR	NR	> G3 AE, 1.9%; G5 AE, 0.4%	Retrospective review across 20 institutions of JRS-SBRTSG
Lagerwaard et al. 2012 (71)	177	T1 [106], T2 [71]	60 Gy/3 fr [61]: peripheral T1 without broad contact with chest wall 60 Gy/5 fr [82]: T1 in broad contact with chest wall or T2 60 Gy/8 fr [34]: central tumours TTD: within 2 weeks	80% IDL	3 years, 93% (LC)	3 years, 84.7%; 5 years, 51.3%	NR	3 years, 9.7% (RR)	3 years, 9.7% (DMR)	$\geq$ G3 pulmonary, 4/177 (2.3%); rib fractures, 5/177 (2.8%); Post-SBRT 30-day mortality 0%	Retrospective analysis of patients in a prospective institutional database

Table 3 (continued)

Table 3 (continued)

Study	Sample size	Patient characteristics [patient number]	PD [patient number]	Prescription point	LC/LPFS	OS	CSS	RR/RFS	DMR/DMFS	Toxicities	Others
Timmerman <i>et al.</i> 2013 (37)	26	T1 [23], T2 [3]	54 Gy/3 fr; TTD: 1.5–2.0 weeks	PD covering >95% PTV	PT only, 2 years, 92.3% (CI, 81.9–100.0%) (LC); PT + involved lobe, 2 years, 80.8% (CI, 65.3–96.3%) (LC)	2 years, 84.4% (CI, 63.7–93.9%)	NR	2 years, 11.7% (CI, 0.0–24.5%) (RR)	2 years, 15.4% (CI, 1.2–29.6%) (DMR)	G3 AE, 4/26 (15.4%); G4–5 AE, 0/26	Phase 2 single arm

All confidence intervals are at 95% unless stated otherwise. SBRT, stereotactic body radiotherapy; PD, prescription dose; LC, local control; LPFS, local progression free survival; OS, overall survival; CSS, cancer specific survival; RR, regional recurrence; RFS, regional-recurrence free survival; DMR, distant metastases recurrence; DMFS, distant metastases free survival; fr, fractions; TTD, total treatment duration; BED, biologically effective dose; CI, confidence interval; NR, not reported; G, grade; IDL, isodose line; AE, adverse events; OAR, organ at risk; EOD, every other day; PTV, primary tumour; PTV, planning target volume.

Emory University demonstrated an incidence of grade ≥ 3 RP of only 3.5% in their cohort of patients with a median age of 85. Interestingly, patients who were not on angiotensin converting enzyme inhibitors (ACE-I) were at a higher risk of RP [odds ratio (OR) 5.83, 95% CI, 1.29–26.32] suggesting that there are complex biological mechanisms underpinning RP (62).

Invariably, normal tissue toxicity is the result of an acute inflammatory response within the microenvironment to radiation injury, through expression and maintenance of inflammatory cytokines, fibrotic cytokines, chemokines and recruitment of inflammatory cells, leading subsequently to scar formation or fibrosis (108,109). Identification and monitoring of blood-borne inflammatory biomarkers such as transforming growth factor β (TGF β), IL-6, Krebs von den Lungen (KL-6) and surfactant protein (SP-D) can potentially account for inter-individual differences in responses to radiation injury beyond clinical, radiological and dosimetric parameters (109,110). Indeed, in an attempt to further stratify patients' risk of RP, Yamashita *et al.* prospectively combined individual pre-treatment blood biomarkers KL-6 and SP-D with presence of interstitial pneumonitis on CT imaging. Despite all patients meeting dose constraints as per JCOG 0403 protocol, they found an increased risk of severe RP in patients with elevated KL-6 [32% (high) *vs.* 3% (low), $P=0.0002$], elevated SP-D [29% (high) *vs.* 3% (low), $P=0.0002$] and interstitial pneumonitis on CT [57% (high) *vs.* 2% (low), $P<0.0001$]. To date, these biomarkers have not been validated in a larger independent cohort prospectively but they demonstrate the clinical benefits of identifying these susceptible, more radiosensitive patients a priori (110). Furthermore, up to 80% of inter-individual differences in normal tissue toxicity can be attributed to genetic differences underpinning inflammatory and DNA damage responses (108,111,112). Discussed in greater detail in the companion review by Tan *et al.* (113), high throughput sequencing techniques can identify common low penetrance allelic variations predictive of a more radiosensitive phenotype. Specific to definitive thoracic radiotherapy, several studies have demonstrated associations between radiation-induced pneumonitis and single nucleotide polymorphisms (SNPs) of heat-shock protein beta-1 (HSPB1) (114), TGF β 1 (115), ataxia-telangiectasia mutated (ATM) and Nijmegen breakage syndrome 1 (NBS1) (116) genes but they have not been validated in large-scale prospective genome-wide association studies (GWAS). Nevertheless, these

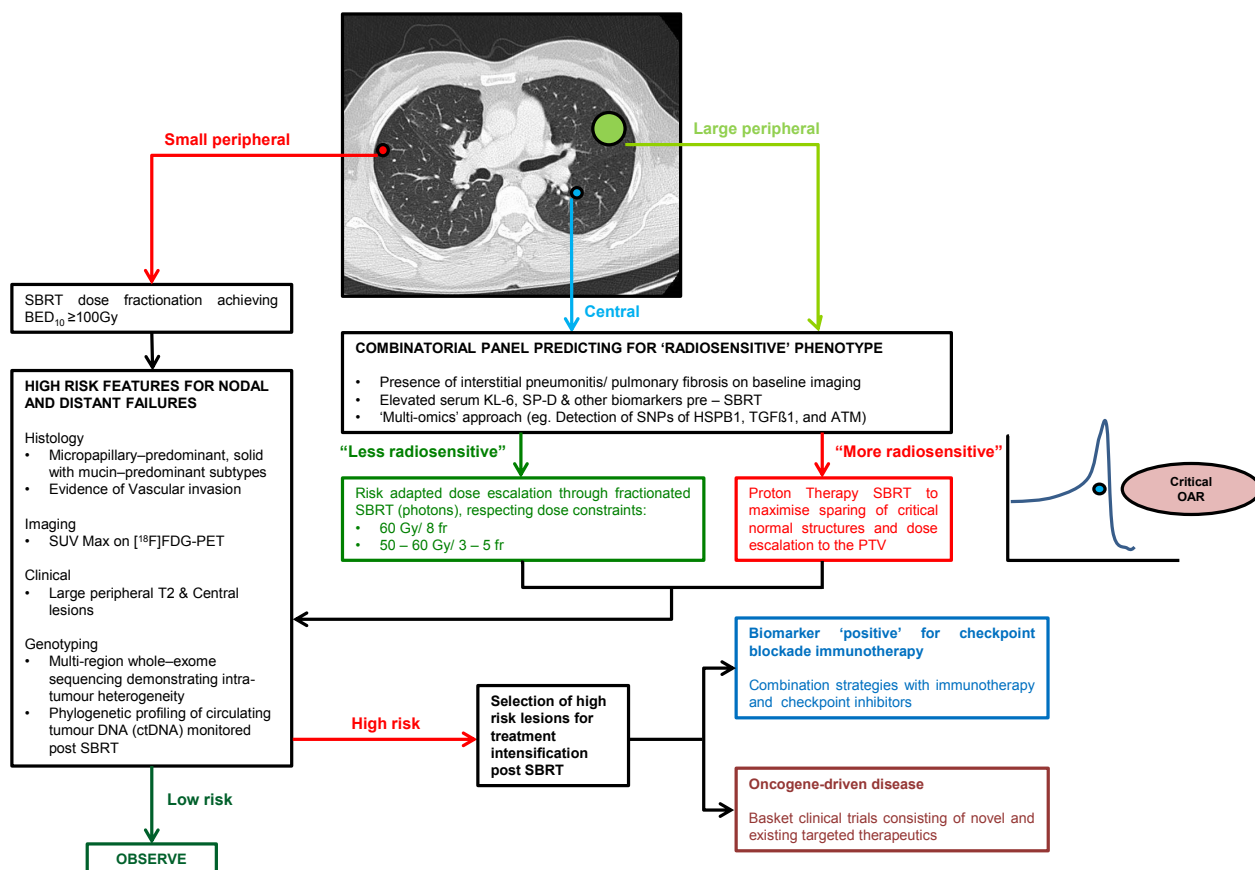


Figure 1 Proposed combinatorial risk-stratification models for predicting “radiosensitive” phenotypes for dose escalation strategies and patients at risk for nodal and distant failure for treatment intensification strategies post SBRT, thereby optimising the therapeutic ratio. SUV, standardised uptake value; KL-6, Krebs von den Lungen; SP-D, surfactant protein D; SNP, single nucleotide polymorphisms; HSPB1, heat-shock protein B1; TGFβ1, transforming growth factor β1; ATM, ataxia-telangiectasia mutated; Fr, fraction; SBRT, stereotactic body radiotherapy; PTV, planning target volume; OAR, organ at risk.

genotyping findings, when integrated with epigenetic factors, post-translational modifications, cell signalling networks and metabolism in an all-encompassing “omics” approach, allow identification of critical pathways and complex interactions crucial to the development of normal tissue toxicity (112). Combined with imaging features, blood-borne biomarkers and functional cellular assays, this integrated predictive model can add a paradigm of biological precision to risk stratification and dose prescription in high risk SBRT involving central tumours or larger ($\geq T2$) peripheral tumours with borderline normal tissue doses; patients predicted to be at risk of toxicities can either be offered a more conservative dose regimen or alternative means of dose escalation can be explored by exploiting the dosimetric advantages of particle therapy, a technology which will be discussed in greater detail shortly.

On the other hand, patients at low risk of toxicities can have their dose escalated further to maximise TCP. This risk-stratified approach is illustrated in *Figure 1*.

Future directions

Moving forward, exciting developments on the horizon offer new strategies and technologies, which can be complementary to and synergistic with lung SBRT. Particle beam therapy (PBT) enables irradiation of tumours at depth while allowing a very sharp dose gradient distal to the target. Initially limited to large teaching institutions, recent innovations have helped to drive down the size, cost and complexity of PBT facilities, making them far more accessible. Examples of these innovations include the vertically arranged proton therapy system in Aizawa

Hospital, Matsumoto, Japan (Sumitomo Heavy Industries, Tokyo, Japan), the S250 (Mevion, Massachusetts, US) with its gantry mounted proton accelerator and superconducting synchrocyclotron and the Radiance 330 (ProTom International, Texas, US) with its modular design allowing customisation based on individual facility needs. On the back of these innovations, the number of PBT centres is expected to rise and it is projected that by 2017, there would be 27 PBT centres in the United States (US) alone (117). While concerns surrounding organ motion and interplay effects in lung PBT remain (118), with further improvements in motion management technology, the superior dosimetry offered by PBT can be harnessed to enhance tumour dose escalation and critical tissue sparing, especially when treating central lung tumours. In addition, particle irradiation may stimulate changes within the tumour microenvironment, which could potentially suppress metastatic processes such as cell migration and invasion (119). So far, early comparisons suggest that hypo-fractionation through PBT may offer additional clinical benefits over SBRT with conventional X-rays. In a systematic review by Chi *et al.* which pooled 72 SBRT studies and 9 single-arm hypo-fractionated PBT studies from 2000 to 2016, before adjusting for potential confounding variables, PBT was associated with improved OS ($P=0.005$) and PFS ($P=0.01$) while significantly reducing rates of $\geq$ grade 3 RP ($P<0.001$), $\geq$ grade 3 chest-wall toxicities ($P=0.03$) and rib fractures ($P<0.001$) (120). As PBT technology continues to evolve, direct comparison studies will be eagerly awaited.

In recent times, immune modulating strategies have dominated the headlines in oncology. The fervent embrace of immunotherapy in NSCLC started with early successes using checkpoint inhibitors in metastatic disease (121-123). In the companion review by Tharmalingam and Hoskin, the authors concluded that SBRT is most systematically immunogenic as demonstrated in both *in vivo* murine models (15,124) and reported clinical cases (125) and would therefore be the ideal candidate for combination with immune modulating strategies (126). This approach will be the subject of investigation in the Dutch PEMBRO-RT study (127) (NCT02492568) but only in the setting of metastatic disease. In early stage disease, nodal and distant failures can be as high as 30% (36,60). Histologic features such as micropapillary-predominant, solid with mucin-predominant subtypes (128,129) and vascular invasion (130), pre-treatment SUV max on ^{18}F -FDG PET (131) and

gene-expression profiles (130,132) can predict for higher risk early stage disease (133) and stratify these patients for treatment intensification with further systemic treatment or combination with immunotherapy. To this end, large-scale genotyping efforts such as the Lung TRACERx Study (134) have provided new insights into tumour evolution and biology. Multi-region whole-exome sequencing of 100 early stage NSCLC in the TRACERx cohort found that intra-tumour heterogeneity, mediated through chromosome instability, was associated with an increased risk of recurrence or death following surgery ($\text{HR}=4.9$, $P=4.4\times 10^{-4}$) (135). Furthermore, owing to the sub-clonal nature of early stage lung cancer relapse and metastasis, tumour-specific phylogenetic profiling of circulating tumour DNA (ctDNA) in serially collected liquid biopsies, was able to quantify sustained presence of sub-clonal single nucleotide variants in ctDNA post-surgery, which preceded subsequent relapse and adjuvant chemotherapy resistance (136). Taken together, high throughput genomic profiling of tumours and ctDNA can be exploited to identify “high risk” early stage NSCLC for treatment intensification following SBRT. This strategy is illustrated in *Figure 1*.

Conclusions

In the past 2 decades, through a series of well-planned clinical trials and advancements in radiotherapy technology, lung SBRT has cemented its place in the management of early stage NSCLC. The era of precision medicine has not only divulged new insights into the biology of this disease but also into inter-individual differences in responses to radiation injury. Going forward, with new tools at our disposal, these insights will inspire new intelligent strategies to further improve our cure rates of early stage NSCLC.

Acknowledgements

Funding: ML Chua is supported by the National Medical Research Council Singapore Transition Award (#NMRC/TA/0030/2014), and the Duke-NUS Oncology Academic Program Proton Research Program.

Footnote

Conflicts of Interest: KL Chua has received speaker honorarium from Varian Medical Systems; ML Chua has received speaker honorarium from Varian Medical Systems,

and research funding from GenomeDx Biosciences. The remaining authors have no conflicts of interest to declare.

References

- Perez CA, Bauer M, Edelstein S, et al. Impact of tumor control on survival in carcinoma of the lung treated with irradiation. *Int J Radiat Oncol Biol Phys* 1986;12:539-47.
- Mehta N, King CR, Agazaryan N, et al. Stereotactic body radiation therapy and 3-dimensional conformal radiotherapy for stage I non-small cell lung cancer: A pooled analysis of biological equivalent dose and local control. *Pract Radiat Oncol* 2012;2:288-95.
- Saunders M, Dische S, Barrett A, et al. Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial. CHART Steering committee. *Radiother Oncol* 1999;52:137-48.
- Nyman J, Hallqvist A, Lund JA, et al. SPACE - A randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC. *Radiother Oncol* 2016;121:1-8.
- Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol* 2007;2:S94-100.
- Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006;24:4833-9.
- Nagata Y, Takayama K, Matsuo Y, et al. Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. *Int J Radiat Oncol Biol Phys* 2005;63:1427-31.
- Uematsu M, Shioda A, Suda A, et al. Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small cell lung cancer: a 5-year experience. *Int J Radiat Oncol Biol Phys* 2001;51:666-70.
- Lo SS, Fakiris AJ, Chang EL, et al. Stereotactic body radiation therapy: a novel treatment modality. *Nat Rev Clin Oncol* 2010;7:44-54.
- Ohri N, Werner-Wasik M, Grills IS, et al. Modeling local control after hypofractionated stereotactic body radiation therapy for stage I non-small cell lung cancer: a report from the Elekta collaborative lung research group. *Int J Radiat Oncol Biol Phys* 2012;84:e379-84.
- Iwata H, Shibamoto Y, Murata R, et al. Estimation of errors associated with use of linear-quadratic formalism for evaluation of biologic equivalence between single and hypofractionated radiation doses: an in vitro study. *Int J Radiat Oncol Biol Phys* 2009;75:482-8.
- Garcia-Barros M, Paris F, Cordon-Cardo C, et al. Tumor response to radiotherapy regulated by endothelial cell apoptosis. *Science* 2003;300:1155-9.
- Fuks Z, Kolesnick R. Engaging the vascular component of the tumor response. *Cancer Cell* 2005;8:89-91.
- Park HJ, Griffin RJ, Hui S, et al. Radiation-induced vascular damage in tumors: implications of vascular damage in ablative hypofractionated radiotherapy (SBRT and SRS). *Radiat Res* 2012;177:311-27.
- Lugade AA, Moran JP, Gerber SA, et al. Local radiation therapy of B16 melanoma tumors increases the generation of tumor antigen-specific effector cells that traffic to the tumor. *J Immunol* 2005;174:7516-23.
- Roberts SA, Hendry JH. A realistic closed-form radiobiological model of clinical tumor-control data incorporating intertumor heterogeneity. *Int J Radiat Oncol Biol Phys* 1998;41:689-99.
- Guckenberger M, Klement RJ, Allgäuer M, et al. Applicability of the linear-quadratic formalism for modeling local tumor control probability in high dose per fraction stereotactic body radiotherapy for early stage non-small cell lung cancer. *Radiother Oncol* 2013;109:13-20.
- Shuryak I, Carlson DJ, Brown JM, et al. High-dose and fractionation effects in stereotactic radiation therapy: Analysis of tumor control data from 2965 patients. *Radiother Oncol* 2015;115:327-34.
- Brown JM, Brenner DJ, Carlson DJ. Dose escalation, not "new biology," can account for the efficacy of stereotactic body radiation therapy with non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2013;85:1159-60.
- Brown JM, Carlson DJ, Brenner DJ. The tumor radiobiology of SRS and SBRT: are more than the 5 Rs involved? *Int J Radiat Oncol Biol Phys* 2014;88:254-62.
- Benedict SH, Yenice KM, Followill D, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. *Med Phys* 2010;37:4078-101.
- Timmerman R, Galvin J, Michalski J, et al. Accreditation and quality assurance for Radiation Therapy Oncology Group: Multicenter clinical trials using Stereotactic Body Radiation Therapy in lung cancer. *Acta Oncol* 2006;45:779-86.

23. Slotman BJ. Stereotactic body radiotherapy for stage I non-small cell lung cancer. *J Radiosurg SBRT* 2011;1:63-9.
24. Nakamura M, Narita Y, Matsuo Y, et al. Geometrical differences in target volumes between slow CT and 4D CT imaging in stereotactic body radiotherapy for lung tumors in the upper and middle lobe. *Med Phys* 2008;35:4142-8.
25. Yamashita H, Takahashi W, Haga A, et al. Stereotactic body radiotherapy for small lung tumors in the University of Tokyo Hospital. *Biomed Res Int* 2014;2014:136513.
26. Mageras GS, Yorke E. Deep inspiration breath hold and respiratory gating strategies for reducing organ motion in radiation treatment. *Semin Radiat Oncol* 2004;14:65-75.
27. Onishi H, Kawakami H, Marino K, et al. A simple respiratory indicator for irradiation during voluntary breath holding: a one-touch device without electronic materials. *Radiology* 2010;255:917-23.
28. Giraud P, Houle A. Respiratory Gating for Radiotherapy: Main Technical Aspects and Clinical Benefits. *ISRN Pulmonol.* 2013;2013:13.
29. Kwa SL, Lebesque JV, Theuws JC, et al. Radiation pneumonitis as a function of mean lung dose: an analysis of pooled data of 540 patients. *Int J Radiat Oncol Biol Phys* 1998;42:1-9.
30. Cheung PC, Yeung LT, Basrur V, et al. Accelerated hypofractionation for early-stage non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2002;54:1014-23.
31. Adebahr S, Collette S, Shash E, et al. LungTech, an EORTC Phase II trial of stereotactic body radiotherapy for centrally located lung tumours: a clinical perspective. *Br J Radiol* 2015;88:20150036.
32. Kimura T, Nagata Y, Harada H, et al. Phase I study of stereotactic body radiation therapy for centrally located stage IA non-small cell lung cancer (JROSG10-1). *Int J Clin Oncol* 2017. [Epub ahead of print].
33. Bezjak A, Paulus R, Gaspar LE, et al. Efficacy and Toxicity Analysis of NRG Oncology/RTOG 0813 Trial of Stereotactic Body Radiation Therapy (SBRT) for Centrally Located Non-Small Cell Lung Cancer (NSCLC). *Int J Radiat Oncol Biol Phys* 2016;96:S8.
34. Onimaru R, Shirato H, Shibata T, et al. Phase I study of stereotactic body radiation therapy for peripheral T2N0M0 non-small cell lung cancer with PTV<100 cc using a continual reassessment method (JCOG0702). *Radiother Oncol* 2015;116:276-80.
35. Videtic GM, Hu C, Singh AK, et al. A Randomized Phase 2 Study Comparing 2 Stereotactic Body Radiation Therapy Schedules for Medically Inoperable Patients With Stage I Peripheral Non-Small Cell Lung Cancer: NRG Oncology RTOG 0915 (NCCTG N0927). *Int J Radiat Oncol Biol Phys* 2015;93:757-64.
36. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010;303:1070-6.
37. Timmerman RD, Paulus R, Pass HI, et al. RTOG 0618: Stereotactic body radiation therapy (SBRT) to treat operable early-stage lung cancer patients. *J Clin Oncol* 2013;31:7523.
38. Rauschenbach BM, Mackowiak L, Malhotra HK. A dosimetric comparison of three-dimensional conformal radiotherapy, volumetric-modulated arc therapy, and dynamic conformal arc therapy in the treatment of non-small cell lung cancer using stereotactic body radiotherapy. *J Appl Clin Med Phys* 2014;15:4898.
39. Sapkaroski D, Osborne C, Knight KA. A review of stereotactic body radiotherapy - is volumetric modulated arc therapy the answer? *J Med Radiat Sci* 2015;62:142-51.
40. Stam B, Peulen H, Guckenberger M, et al. Dose to heart substructures is associated with non-cancer death after SBRT in stage I-II NSCLC patients. *Radiother Oncol* 2017;123:370-5.
41. Ong CL, Dahele M, Slotman BJ, et al. Dosimetric impact of the interplay effect during stereotactic lung radiation therapy delivery using flattening filter-free beams and volumetric modulated arc therapy. *Int J Radiat Oncol Biol Phys* 2013;86:743-8.
42. Verbakel WF, Senan S, Cuijpers JP, et al. Rapid delivery of stereotactic radiotherapy for peripheral lung tumors using volumetric intensity-modulated arcs. *Radiother Oncol* 2009;93:122-4.
43. Timmerman R, Papiez L, McGarry R, et al. Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer. *Chest* 2003;124:1946-55.
44. McGarry RC, Papiez L, Williams M, et al. Stereotactic body radiation therapy of early-stage non-small-cell lung carcinoma: phase I study. *Int J Radiat Oncol Biol Phys* 2005;63:1010-5.
45. Stahl JM, Ross R, Harder EM, et al. The Effect of Biologically Effective Dose and Radiation Treatment Schedule on Overall Survival in Stage I Non-Small Cell Lung Cancer Patients Treated With Stereotactic Body Radiation Therapy. *Int J Radiat Oncol Biol Phys* 2016;96:1011-20.
46. Koshy M, Malik R, Weichselbaum RR, et al. Increasing radiation therapy dose is associated with improved survival

- in patients undergoing stereotactic body radiation therapy for stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2015;91:344-50.
47. Onimaru R, Fujino M, Yamazaki K, et al. Steep dose-response relationship for stage I non-small-cell lung cancer using hypofractionated high-dose irradiation by real-time tumor-tracking radiotherapy. *Int J Radiat Oncol Biol Phys* 2008;70:374-81.
 48. Onimaru R, Onishi H, Shibata T, et al. Phase I study of stereotactic body radiation therapy for peripheral T2N0M0 non-small cell lung cancer (JCOG0702): Results for the group with PTV 100cc. *Radiother Oncol* 2017;122:281-5.
 49. Haasbeek CJ, Lagerwaard FJ, Slotman BJ, et al. Outcomes of stereotactic ablative radiotherapy for centrally located early-stage lung cancer. *J Thorac Oncol* 2011;6:2036-43.
 50. Nishimura S, Takeda A, Sanuki N, et al. Toxicities of organs at risk in the mediastinal and hilar regions following stereotactic body radiotherapy for centrally located lung tumors. *J Thorac Oncol* 2014;9:1370-6.
 51. Corradetti MN, Haas AR, Rengan R. Central-airway necrosis after stereotactic body-radiation therapy. *N Engl J Med* 2012;366:2327-9.
 52. Wulf J, Haedinger U, Oppitz U, et al. Stereotactic radiotherapy for primary lung cancer and pulmonary metastases: a noninvasive treatment approach in medically inoperable patients. *Int J Radiat Oncol Biol Phys* 2004;60:186-96.
 53. Hof H, Muentzer M, Oetzel D, et al. Stereotactic single-dose radiotherapy (radiosurgery) of early stage nonsmall-cell lung cancer (NSCLC). *Cancer* 2007;110:148-55.
 54. Hara R, Itami J, Kondo T, et al. Clinical outcomes of single-fraction stereotactic radiation therapy of lung tumors. *Cancer* 2006;106:1347-52.
 55. Le QT, Loo BW, Ho A, et al. Results of a phase I dose-escalation study using single-fraction stereotactic radiotherapy for lung tumors. *J Thorac Oncol* 2006;1:802-9.
 56. Zhang J, Yang F, Li B, et al. Which is the optimal biologically effective dose of stereotactic body radiotherapy for Stage I non-small-cell lung cancer? A meta-analysis. *Int J Radiat Oncol Biol Phys* 2011;81:e305-16.
 57. Guckenberger M. Dose and Fractionation in Stereotactic Body Radiation Therapy for Stage I Non-Small Cell Lung Cancer: Lessons Learned and Where Do We Go Next? *Int J Radiat Oncol Biol Phys* 2015;93:765-8.
 58. Fakiris AJ, McGarry RC, Yiannoutsos CT, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. *Int J Radiat Oncol Biol Phys* 2009;75:677-82.
 59. Baumann P, Nyman J, Hoyer M, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. *J Clin Oncol* 2009;27:3290-6.
 60. Timmerman RD, Hu C, Michalski J, et al. Long-term Results of RTOG 0236: A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Medically Inoperable Stage I Non-Small Cell Lung Cancer. *Int J Radiat Oncol Biol Phys* 2014;90:S30.
 61. Videtic GM, Stephans K, Reddy C, et al. Intensity-modulated radiotherapy-based stereotactic body radiotherapy for medically inoperable early-stage lung cancer: excellent local control. *Int J Radiat Oncol Biol Phys* 2010;77:344-9.
 62. Cassidy RJ, Patel PR, Zhang X, et al. Stereotactic Body Radiotherapy for Early-stage Non-small-cell Lung Cancer in Patients 80 Years and Older: A Multi-center Analysis. *Clin Lung Cancer* 2017. [Epub ahead of print].
 63. Ricardi U, Filippi AR, Guarneri A, et al. Stereotactic body radiation therapy for early stage non-small cell lung cancer: results of a prospective trial. *Lung Cancer* 2010;68:72-7.
 64. Fritz P, Kraus HJ, Mühlnickel W, et al. Stereotactic, single-dose irradiation of stage I non-small cell lung cancer and lung metastases. *Radiat Oncol* 2006;1:30.
 65. Koto M, Takai Y, Ogawa Y, et al. A phase II study on stereotactic body radiotherapy for stage I non-small cell lung cancer. *Radiother Oncol* 2007;85:429-34.
 66. Onishi H, Yoshiyuki S, Yasuo M, et al. Japanese Multi-institutional Study of Stereotactic Body Radiation Therapy for More Than 2000 Patients With Stage I Non-Small Cell Lung Cancer. *Int J Radiat Oncol Biol Phys* 2013;87:S9-S10.
 67. Nagata Y, Hiraoka M, Shibata T, et al. Prospective Trial of Stereotactic Body Radiation Therapy for Both Operable and Inoperable T1N0M0 Non-Small Cell Lung Cancer: Japan Clinical Oncology Group Study JCOG0403. *Int J Radiat Oncol Biol Phys* 2015;93:989-96.
 68. Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? *Int J Radiat Oncol Biol Phys* 2011;81:1352-8.
 69. Eriguchi T, Takeda A, Sanuki N, et al. Stereotactic body radiotherapy for operable early-stage non-small cell lung

- cancer. *Lung Cancer* 2017;109:62-7.
70. Onishi H, Shioyama Y, Matsumoto Y, et al. Japanese Multi-institutional Study of Stereotactic Body Radiation Therapy for 661 Medically Operable Patients With Stage I Non-Small Cell Lung Cancer. *Int J Radiat Oncol Biol Phys* 2015;93:S187.
 71. Lagerwaard FJ, Versteegen NE, Haasbeek CJ, et al. Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage I non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2012;83:348-53.
 72. Palma D, Visser O, Lagerwaard FJ, et al. Treatment of stage I NSCLC in elderly patients: a population-based matched-pair comparison of stereotactic radiotherapy versus surgery. *Radiother Oncol* 2011;101:240-4.
 73. Whitson BA, Groth SS, Duval SJ, et al. Surgery for early-stage non-small cell lung cancer: a systematic review of the video-assisted thoracoscopic surgery versus thoracotomy approaches to lobectomy. *Ann Thorac Surg* 2008;86:2008-16; discussion 2016-8.
 74. Pezzi CM, Mallin K, Mendez AS, et al. Ninety-day mortality after resection for lung cancer is nearly double 30-day mortality. *J Thorac Cardiovasc Surg* 2014;148:2269-77.
 75. Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol* 2015;16:630-7.
 76. Lagerwaard FJ, Aaronson NK, Gundy CM, et al. Patient-reported quality of life after stereotactic ablative radiotherapy for early-stage lung cancer. *J Thorac Oncol* 2012;7:1148-54.
 77. Louie AV, van Werkhoven E, Chen H, et al. Patient reported outcomes following stereotactic ablative radiotherapy or surgery for stage IA non-small-cell lung cancer: Results from the ROSEL multicenter randomized trial. *Radiother Oncol* 2015;117:44-8.
 78. Crabtree TD, Denlinger CE, Meyers BF, et al. Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2010;140:377-86.
 79. Wink KCJ, van Baardwijk A, Troost EGC, et al. Nodal recurrence after stereotactic body radiotherapy for early stage non-small cell lung cancer: Incidence and proposed risk factors. *Cancer Treat Rev* 2017;56:8-15.
 80. Bernstein MB, Krishnan S, Hodge JW, et al. Immunotherapy and stereotactic ablative radiotherapy (ISABR): a curative approach? *Nat Rev Clin Oncol* 2016;13:516-24.
 81. Tournoy KG, Keller SM, Annema JT. Mediastinal staging of lung cancer: novel concepts. *Lancet Oncol* 2012;13:e221-9.
 82. Gao SJ, Kim AW, Puchalski JT, et al. Indications for invasive mediastinal staging in patients with early non-small cell lung cancer staged with PET-CT. *Lung Cancer* 2017;109:36-41.
 83. Amendola BE, Amendola MA, Perez N, et al. Local failure after primary radiotherapy in lung cancer: Is there a role for SBRT? *Rep Pract Oncol Radiother* 2015;20:440-5.
 84. Hamaji M, Chen F, Matsuo Y, et al. Treatment and Prognosis of Isolated Local Relapse after Stereotactic Body Radiotherapy for Clinical Stage I Non-Small-Cell Lung Cancer: Importance of Salvage Surgery. *J Thorac Oncol* 2015;10:1616-24.
 85. Nishimura S, Takeda A, Sanuki N, et al. Dose-Escalated Stereotactic Body Radiotherapy (SBRT) as a Salvage Treatment for Two Cases with Relapsed Peripheral Lung Cancer After Initial SBRT. *J Thorac Oncol* 2015;10:e69-71.
 86. Hearn JW, Videtic GM, Djemil T, et al. Salvage stereotactic body radiation therapy (SBRT) for local failure after primary lung SBRT. *Int J Radiat Oncol Biol Phys* 2014;90:402-6.
 87. Neri S, Takahashi Y, Terashi T, et al. Surgical treatment of local recurrence after stereotactic body radiotherapy for primary and metastatic lung cancers. *J Thorac Oncol* 2010;5:2003-7.
 88. Kang KH, Okoye CC, Patel RB, et al. Complications from Stereotactic Body Radiotherapy for Lung Cancer. *Cancers (Basel)* 2015;7:981-1004.
 89. Karlsson K, Nyman J, Baumann P, et al. Retrospective cohort study of bronchial doses and radiation-induced atelectasis after stereotactic body radiation therapy of lung tumors located close to the bronchial tree. *Int J Radiat Oncol Biol Phys* 2013;87:590-5.
 90. Abelson JA, Murphy JD, Loo BW Jr, et al. Esophageal tolerance to high-dose stereotactic ablative radiotherapy. *Dis Esophagus* 2012;25:623-9.
 91. Evans JD, Gomez DR, Amini A, et al. Aortic dose constraints when reirradiating thoracic tumors. *Radiother Oncol* 2013;106:327-32.
 92. Hoppe BS, Laser B, Kowalski AV, et al. Acute skin toxicity following stereotactic body radiation therapy for stage I non-small-cell lung cancer: who's at risk? *Int J Radiat Oncol Biol Phys* 2008 ;72:1283-6.
 93. Nambu A, Onishi H, Aoki S, et al. Rib fracture after stereotactic radiotherapy on follow-up thin-section

- computed tomography in 177 primary lung cancer patients. *Radiat Oncol* 2011;6:137.
94. Stam B, van der Bijl E, Peulen H, et al. Dose-effect analysis of radiation induced rib fractures after thoracic SBRT. *Radiother Oncol* 2017;123:176-81.
 95. Andolino DL, Forquer JA, Henderson MA, et al. Chest wall toxicity after stereotactic body radiotherapy for malignant lesions of the lung and liver. *Int J Radiat Oncol Biol Phys* 2011;80:692-7.
 96. Seppenwoolde Y, De Jaeger K, Boersma LJ, et al. Regional differences in lung radiosensitivity after radiotherapy for non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2004;60:748-58.
 97. Tucker SL, Jin H, Wei X, et al. Impact of toxicity grade and scoring system on the relationship between mean lung dose and risk of radiation pneumonitis in a large cohort of patients with non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2010;77:691-8.
 98. Forquer JA, Fakiris AJ, Timmerman RD, et al. Brachial plexopathy from stereotactic body radiotherapy in early-stage NSCLC: dose-limiting toxicity in apical tumor sites. *Radiother Oncol* 2009;93:408-13.
 99. Shultz DB, Trakul N, Maxim PG, et al. Vagal and recurrent laryngeal neuropathy following stereotactic ablative radiation therapy in the chest. *Pract Radiat Oncol* 2014;4:272-8.
 100. Ohnishi K, Shiroyama Y, Nomoto S, et al. Spontaneous pneumothorax after stereotactic radiotherapy for non-small-cell lung cancer. *Jpn J Radiol* 2009;27:269-74.
 101. Stephans KL, Djemil T, Reddy CA, et al. Comprehensive analysis of pulmonary function Test (PFT) changes after stereotactic body radiotherapy (SBRT) for stage I lung cancer in medically inoperable patients. *J Thorac Oncol* 2009;4:838-44.
 102. Guckenberger M, Baier K, Polat B, et al. Dose-response relationship for radiation-induced pneumonitis after pulmonary stereotactic body radiotherapy. *Radiother Oncol* 2010;97:65-70.
 103. Guckenberger M, Kestin LL, Hope AJ, et al. Is there a lower limit of pretreatment pulmonary function for safe and effective stereotactic body radiotherapy for early-stage non-small cell lung cancer? *J Thorac Oncol* 2012;7:542-51.
 104. Ito H, Nakayama H, Tsuboi M, et al. Subpleural honeycombing on high resolution computed tomography is risk factor for fatal pneumonitis. *Ann Thorac Surg* 2011;91:874-8.
 105. Sanuki N, Ono A, Komatsu E, et al. Association of computed tomography-detected pulmonary interstitial changes with severe radiation pneumonitis for patients treated with thoracic radiotherapy. *J Radiat Res* 2012;53:110-6.
 106. Kazerooni EA, Martinez FJ, Flint A, et al. Thin-section CT obtained at 10-mm increments versus limited three-level thin-section CT for idiopathic pulmonary fibrosis: correlation with pathologic scoring. *AJR Am J Roentgenol* 1997;169:977-83.
 107. Tsujino K, Hashimoto T, Shimada T, et al. Combined analysis of V20, VS5, pulmonary fibrosis score on baseline computed tomography, and patient age improves prediction of severe radiation pneumonitis after concurrent chemoradiotherapy for locally advanced non-small-cell lung cancer. *J Thorac Oncol* 2014;9:983-90.
 108. Barnett GC, West CM, Dunning AM, et al. Normal tissue reactions to radiotherapy: towards tailoring treatment dose by genotype. *Nat Rev Cancer* 2009;9:134-42.
 109. Kong FM, Ao X, Wang L, et al. The use of blood biomarkers to predict radiation lung toxicity: a potential strategy to individualize thoracic radiation therapy. *Cancer Control* 2008;15:140-50.
 110. Yamashita H, Kobayashi-Shibata S, Terahara A, et al. Prescreening based on the presence of CT-scan abnormalities and biomarkers (KL-6 and SP-D) may reduce severe radiation pneumonitis after stereotactic radiotherapy. *Radiat Oncol* 2010;5:32.
 111. Turesson I, Nyman J, Holmberg E, et al. Prognostic factors for acute and late skin reactions in radiotherapy patients. *Int J Radiat Oncol Biol Phys* 1996;36:1065-75.
 112. Herskind C, Talbot CJ, Kerns SL, et al. Radiogenomics: A systems biology approach to understanding genetic risk factors for radiotherapy toxicity? *Cancer Lett* 2016;382:95-109.
 113. Tan JS, Liu X, Chua KL. Exploiting molecular genomics in precision radiation oncology: a marriage of biological and physical precision. *Chin Clin Oncol* 2017. [Epub ahead of print].
 114. Pang Q, Wei Q, Xu T, et al. Functional promoter variant rs2868371 of HSPB1 is associated with risk of radiation pneumonitis after chemoradiation for non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2013;85:1332-9.
 115. Yuan X, Liao Z, Liu Z, et al. Single nucleotide polymorphism at rs1982073:T869C of the TGFbeta 1 gene is associated with the risk of radiation pneumonitis in patients with non-small-cell lung cancer treated with

- definitive radiotherapy. *J Clin Oncol* 2009;27:3370-8.
116. Zhang L, Wang L, Yang M, et al. Association of DNA Repair and Inflammatory Cytokines Gene Polymorphisms With Radiation-Induced Toxicity in Lung Cancer. *Int J Radiat Oncol Biol Phys* 2007;69:S60-1.
 117. 27 U.S. Proton Therapy Centers Expected by 2017. Available online: <https://www.itnonline.com/article/27-us-proton-therapy-centers-expected-2017>
 118. De Ruyscher D, Sterpin E, Haustermans K, et al. Tumour Movement in Proton Therapy: Solutions and Remaining Questions: A Review. *Cancers (Basel)* 2015;7:1143-53.
 119. Ogata T, Teshima T, Kagawa K, et al. Particle irradiation suppresses metastatic potential of cancer cells. *Cancer Res* 2005;65:113-20.
 120. Chi A, Chen H, Wen S, et al. Comparison of particle beam therapy and stereotactic body radiotherapy for early stage non-small cell lung cancer: A systematic review and hypothesis-generating meta-analysis. *Radiother Oncol* 2017;123:346-54.
 121. Dempke WC, Fenchel K. Pembrolizumab as first-line treatment for non-small cell lung cancer—a game changer? *Transl Lung Cancer Res* 2016;5:538-42.
 122. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N Engl J Med* 2016;375:1823-33.
 123. Morgensztern D, Herbst RS. Nivolumab and Pembrolizumab for Non-Small Cell Lung Cancer. *Clin Cancer Res* 2016;22:3713-7.
 124. Dewan MZ, Galloway AE, Kawashima N, et al. Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. *Clin Cancer Res* 2009;15:5379-88.
 125. Postow MA, Callahan MK, Barker CA, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. *N Engl J Med* 2012;366:925-31.
 126. Tharmalingam H, Hoskin PJ. The optimism surrounding stereotactic body radiation therapy and immunomodulation. *Chin Clin Oncol* 2017;6:S9.
 127. Pembrolizumab After SBRT Versus Pembrolizumab Alone in Advanced NSCLC (PEMBRO-RT). Available online: <https://clinicaltrials.gov/ct2/show/NCT02492568>
 128. Russell PA, Wainer Z, Wright GM, et al. Does lung adenocarcinoma subtype predict patient survival?: A clinicopathologic study based on the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary lung adenocarcinoma classification. *J Thorac Oncol* 2011;6:1496-504.
 129. Leeman JE, Rimner A, Montecalvo J, et al. Histologic Subtype in Core Lung Biopsies of Early-Stage Lung Adenocarcinoma is a Prognostic Factor for Treatment Response and Failure Patterns After Stereotactic Body Radiation Therapy. *Int J Radiat Oncol Biol Phys* 2017;97:138-45.
 130. Harpole DH Jr, Herndon JE 2nd, Wolfe WG, et al. A prognostic model of recurrence and death in stage I non-small cell lung cancer utilizing presentation, histopathology, and oncoprotein expression. *Cancer Res* 1995;55:51-6.
 131. Kohutek ZA, Wu AJ, Zhang Z, et al. FDG-PET maximum standardized uptake value is prognostic for recurrence and survival after stereotactic body radiotherapy for non-small cell lung cancer. *Lung Cancer* 2015;89:115-20.
 132. Beer DG, Kardia SL, Huang CC, et al. Gene-expression profiles predict survival of patients with lung adenocarcinoma. *Nat Med* 2002;8:816-24.
 133. Taunk NK, Rimner A, Culligan M, et al. Immunotherapy and radiation therapy for operable early stage and locally advanced non-small cell lung cancer. *Transl Lung Cancer Res* 2017;6:178-85.
 134. Jamal-Hanjani M, Hackshaw A, Ngai Y, et al. Tracking genomic cancer evolution for precision medicine: the lung TRACERx study. *PLoS Biol* 2014;12:e1001906.
 135. Jamal-Hanjani M, Wilson GA, McGranahan N, et al. Tracking the Evolution of Non-Small-Cell Lung Cancer. *N Engl J Med* 2017;376:2109-21.
 136. Abbosh C, Birkbak NJ, Wilson GA, et al. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. *Nature* 2017;545:446-51.

Cite this article as: Chua KL, Sin I, Fong KW, Chua ML, Onishi H. Stereotactic body radiotherapy for early stage lung cancer—historical developments and future strategies. *Chin Clin Oncol* 2017;6(Suppl 2):S20. doi: 10.21037/cco.2017.08.02