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Reduced fractionation in lung cancer patients treated with curative-intent radiotherapy during the COVID-19 pandemic

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Introduction

The World Health Organisation (WHO) declared COVID-19, the disease caused by the 2019 novel coronavirus SARS-CoV-2, a pandemic on the 11th of March 2020. During the acute crisis, there will be unprecedented demands on the NHS as a whole and a major impact on cancer services in the UK.

Approximately 48,800 new patients are diagnosed with lung cancer each year in the UK and >50% require radiotherapy treatment. The lung cancer population requiring active treatment with chemotherapy or radiotherapy have been classified as 'extremely vulnerable' and many of our patients who have completed treatment would also be encompassed in this category due to co-existing severe COPD (FEV1 <50% predicted) [1,2]. In addition, a significant proportion of our patients not captured by this definition would still be at significant increased risk of hospital admission and mortality related to COVID-19 due to impaired respiratory function following prior treatment. There is therefore is a need to mitigate the risks of their anti-cancer treatments by addressing risks associated with multiple visits to hospital, treatment-induced immunosuppression, and radiation-associated lung injury. This means adapting our current treatment protocols rapidly to reflect the shifting risk-benefit ratio and diminished resources. In addition, the impact of this pandemic is likely to last for a significant length of time beyond resumption of normal services. This is due to the anticipated backlog of patients diagnosed with lung cancer and the increased demands on the radiotherapy departments (e.g. due to the deferral of radiotherapy in breast and prostate cancer patients).

General guidance on delivery of radiotherapy during the COVID-19 pandemic has been provided by NICE [3]. They recommend discussing alternative dose-fractionation schedules or radiotherapy techniques. However, it should be acknowledged that the timing and ability to implement changes to dose/fractionation schedules will vary depending on resources and technology available (e.g. daily on-line CBCT) and current capabilities (e.g. SABR).

The objective of this document is to identify reduced-fractionation and curative-intent radiotherapy regimes in lung cancer, assess their evidence base, and provide organs-at-risk (OAR) dose constraints. Systematic reviews and relevant papers were identified by a group of UK clinical oncologists through a PubMed search between 20/3/20 and 30/3/20. We also included published and unpublished audits of hypofractionated regimes from UK centres. The aims are: 1) to reduce hospital visits and limit exposure to SARS-CoV-2 of patients having curative-intent radiotherapy for lung cancer; and 2) to increase radiotherapy service capacity for operable patients with stage I-III lung cancer who may not be able to have surgery during the pandemic.

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Early stage NSCLC

SABR offers departments the option of treating early-stage NSCLC patients with high doses and short fractionation schedules. We outline the evidence for further reduction in fraction number and provide links for dose constraints and protocols to deliver these treatments. We also outline the evidence for hypofractionation (beyond 55 Gy in 20 fractions) for central/ultracentral early-stage NSCLC not suitable for SABR due to OAR constraints being exceeded.

1. Single-fraction SABR

Advice

- Consider 30Gy to 34Gy in a single fraction (30-34Gy/1 fraction) in patients with tumours that are ≤2cm, >1cm from the chest wall, and are outside of the no-fly zone. This is in keeping with the current NCCN guidelines[1].

Evidence

Single-fraction schedules of 30-34Gy have been compared to multi-fraction SABR in two phase 2 studies (RTOG 0915, Roswell Park) [2-4]. Local control rate, progression-free survival (PFS), and overall survival (OS), as well as late toxicity and quality of life, were comparable between single-fraction and multi-fraction SABR regimens. Chest wall toxicity did not exceed grade 2 in either arm of both studies. A retrospective study including 146 lesions showed that grade 2-4 chest wall toxicity was 30.6% for lesions abutting the chest wall, 8.2% for tumours ≤1 cm from the chest wall, and 3.8% for tumours 1 to 2 cm from the chest wall [5]. Overall grade ≥3 chest wall toxicity was 1.4%.

Limitations

- A range of SABR dose/fractionation schedules have been described, but no single regimen has been established as the standard of care.
- Evidence is based on phase 2 data only where the number treated within 2cm of the chest wall is very small.

Practical Considerations

- Only centres with prior experience of delivering lung SABR should offer single-fraction SABR
- Patients considered for single-fraction SABR are those typically treated with 54Gy in 3 fractions, rather than 55Gy in 5 fractions
- It is advised only to consider tumours that are moving less than 1cm after appropriate motion management on 4DCT imaging
- The dose constraints recommended are those set out in the RTOG 0915 study (see Tables 1 and 2)

Table 1. Dose Gradient Requirements Based on Target Volume (from NRG Oncology RTOG 0915 protocol)

PTV Volume (cc)	Ratio of Prescription Isodose Volume to the PTV Volume		Ratio of 50% Prescription Isodose Volume to the PTV Volume, $R_{50\%}$		Maximum Dose (in % of dose prescribed) @ 2 cm from PTV in Any Direction, D_{2cm} (%)		Percentage of Lung Receiving 20Gy Total or More, V_{20} (%)	
	Deviation		Deviation		Deviation		Deviation	
	None	Minor	None	Minor	None	Minor	None	Minor
1.8	<1.2	<1.5	<5.9	<7.5	<50.0	<57.0	<10	<15
3.8	<1.2	<1.5	<5.5	<6.5	<50.0	<57.0	<10	<15
7.4	<1.2	<1.5	<5.1	<6.0	<50.0	<58.0	<10	<15
13.2	<1.2	<1.5	<4.7	<5.8	<50.0	<58.0	<10	<15
22.0	<1.2	<1.5	<4.5	<5.5	<54.0	<63.0	<10	<15
34.0	<1.2	<1.5	<4.3	<5.3	<58.0	<68.0	<10	<15
50.0	<1.2	<1.5	<4.0	<5.0	<62.0	<77.0	<10	<15
70.0	<1.2	<1.5	<3.5	<4.8	<66.0	<86.0	<10	<15
95.0	<1.2	<1.5	<3.3	<4.4	<70.0	<89.0	<10	<15
126.0	<1.2	<1.5	<3.1	<4.0	<73.0	<91.0	<10	<15
163.0	<1.2	<1.5	<2.9	<3.7	<77.0	<94.0	<10	<15

PTV: planning target volume

Table 2. Organ dose-volume limits for 30-34Gy single fraction (From NRG Oncology RTOG 0915)

Serial Tissue	Volume (cc)	**Volume Max (Gy)**	**Max Point Dose (Gy)**
Spinal Cord	<0.35 <1.2	10 7	14
Oesophagus	<5	11.9	15.4
Brachial Plexus	<3	14	17.5
Heart/Pericardium	<15	16	22
Great vessels	<10	31	37
Trachea and Large Bronchus	<4	10.5	20.2
Rib	<1	22	30
Skin	<10	23	26
Stomach	<10	11.2	12.4
Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**	
Lung (Right & Left)	1500	7	
Lung (Right & Left)	1000	7.4	

2. SABR for tumours within 2.5 cm of the chest wall

Advice

- Consider 3-fraction regimes (e.g. 54Gy/3 fractions)
- Where the PTV abuts or overlaps the chest wall consider 54Gy/3 fractions or a reduced dose to minimise toxicity (e.g. 48Gy/3 fractions)

Evidence

The rate of grade 3 chest wall toxicity with SABR from a large meta-analysis (combining several different dose and fractionations) is 1.2% [6]. Individual papers have found that the tumour to chest wall distance is a significant factor, as well as the maximum dose (Dmax) and volume of chest wall receiving 30Gy (V30) [7-10]. Multi-fraction retrospective data specifically looking at patients with tumours near the chest wall are shown in Table 3. Where the gross tumour volume (GTV) is within 2.5cm of the chest wall, no increased risk was seen with 3 fractions compared to 5 fractions (1.6% compared to 3.2% respectively) [9]. Where the PTV is abutting the chest wall, data from Andolino et al suggest that 48Gy/3 fractions has a lower toxicity than 54Gy/3 fractions [7].

Table 3. Dose, fractionation, tumour to chest wall distance and rate of toxicity

Paper	Number (n)	Dose/fx	BED_3 Gy	BED_{10} Gy	GTV to CWD (cm)	Rate of toxicity
Andolino [7]	18	54/3 (median)	378	151	0.1	100% any grade
Andolino [7]	61	48/3	304	125	0.2	0% any grade
Asai [8]	116	48/4	240	106	2 (0.3 – 6.2)	24.1% rib fracture, 0.86% G3
Bongers [9]	183	60/3	460	180	<2.5 85.5%*	Any grade CWP: 10.4% G3 CWP: 1.6%
Bongers [9]	187	60/5	300	132	<2.5 91%*	Any grade CWP: 14.4% G3 CWP: 3.2%
Bongers [9]	73	60/8	210	105	<2.5 71.4%*	Any grade CWP: 15% G3 CWP: 1.4%
Nambu [10]	95	48/4	240	106	0.6 (0 - 5.3)	G3 CWP 0%
Nambu [10]	45	60/10	180	96	0.6 (0 - 5.3)	G3 CWP 0%
Nambu [10]	37	70/10	233.3	119	0.6 (0 - 5.3)	G3 CWP 0%

CWD: chest wall distance, CWP: chest wall pain, BED: biological effective dose, GTV: gross tumour volume , G: grade

* Percentage of patients with tumours within 2.5cm of the chest wall

Limitations

- The effect of fractionation schedules on chest wall toxicity has not been investigated in prospective trials.

Practical Considerations

- Suggested chest wall dose constraints for 3 fraction schedules are D0.5cc<60Gy, D5cc<40Gy and V30<30cc (Tables 4.1 and 4.2)

Table 4.1. Biological effective dose, Dmax to chest wall and ribs

Paper	Number (n)	Dose/fx	BED_3 Gy	BED_{10} Gy	Dmax CW (Gy)	Dmax rib (Gy)	Rate of toxicity
Andolino [7]	18	54/3	378	151	64	64	100% any grade, worst possible G3 rate 16.6%
Andolino [7]	61	48/3	304	125	57	52	0% any grade
Taremi [11]	29	54/3 60/3*	378 460	151 180	-	50.2	No rib fracture
	17	54/3 60/3*	378 460	151 180	-	63.7	Rib fracture
	21	54/3 60/3*	378 460	151 180	-	62.8	CW pain
	25	54/3 60/3*	378 460	151 180	-	47.2	No CW pain

- CW: chest wall, fx: fractions, BED: biological effective dose
- *unable to separate number of patients by fractionation as data not available in paper

Table 4.2. Volumetric constraints to the chest wall

Paper	Number (n)	Dose(Gy)/fx (median)	BED_3 Gy	BED_{10} Gy	Dose constraint	Toxicity endpoint
Andolino [7]	347 lesions	18–72/2–5 (54/3)	378	151	D15Gy <240cc D20Gy <130cc D30Gy <40cc D40Gy < 15cc	Limits CW toxicity (any grade)to 30%
					D5cc 40Gy	Predicts 10% CW tox
					D15cc 40Gy	Predicts 30% CW tox
					Dmax >50Gy	Significantly increases risk of CW pain and rib fracture
Pettersson [12]	33	45/3	270	112.5	D2cc < 21 Gy	0% rib fracture
					D2cc < 27.2 Gy	5% rib fracture
					D2cc < 49.8 Gy	50% rib fracture
Taremi [11]	46	54/3	378	151	D0.5cc 60 Gy	50% rib fracture
		60/3*	460	180		
Dunlap [13]	60	21-60/3-5 (60/3)	460	180	V30 (30cc)	G2 CWP 30% if V30>35cc
Mutter [14]	126	40-60/3-5 (54/3)	378	151	V30 (70cc)	G2 CWP 27.8% correlated with V30 >70cc
Stephans [15]	45	60/3	460	180	V30 <30cc	G2 CWP 10-15% if V30<30cc
Welsh [16]	265	50/4	258.3	112.5	V30 <30cc	If V30<30cc G2 CWP rate 2.7%

CW: chest wall, fx: fraction

*unable to separate number of patients by fractionation as data not available in paper

3. SABR for moderately central tumours

Advice

- Consider 50Gy/5 fractions in moderately central tumours

Evidence

Moderately central early-stage NSCLC is defined as a lesion within 2 cm of the bronchial tree, trachea, major vessels, oesophagus, heart, pericardium, or brachial plexus, or PTV abutting mediastinal pleura or pericardium, excluding ultra-central disease. An ultracentral lesion is where the PTV abuts either the main bronchi or trachea.

Two fractionations are commonly used:

- 4-5 fractions as per ASTRO guidelines (based largely on studies using a total dose of 45-50Gy) [17]
- 8 fractions as per UK SABR consortium (total dose 60Gy) [18]

Retrospective studies show similar grade 3 or above toxicity rates between 0 and 7.7%, and local control rates between 77.6 - 95%. There is a lack of prospective evidence to suggest which regime is superior. The safest arm in the prospective RTOG 0813 trial was the 50Gy/5 fractions cohort with no ≥ grade 3 toxic events. 50Gy in 5 fractions has been used in Glasgow based on the RTOG 0813 dose constraints [19]. In a study of 50 patients, there was a 4% grade 3 toxicity rate and a median OS of 27 months, which is consistent with other published literature (Table 5). 50Gy/4 fractions has also been used in North America but lacks prospective trial data and dose constraints.

Table 5. Dose fractionation for moderately central early-stage NSCLC

Fractionation	Tumour BED_{10} Gy	OARs BED_3 Gy	Risk of ≥G3 toxicity	Tumour control	Number (n)	References
60/8	105	210	6.3%	mOS 47 months, 3 yr LCR 92.6%	63	Haasbeek [20]
			Unknown G3 rate, but 0% G4 toxicity	mOS, n/a, 4 yr LCR 77.8%*	9	Taremi [21]
			6.4%	mOS 38 months, LCR n/a	80	Tekatli [22]
50/5	100	216.67	4% (10% risk of chest infection 90 days post SABR)	mOS 27 months, 2 yr LCR 77.6%	50	Rulach [19]
			0%	mOS NR, LCR 100%	10	Olsen [23]
			0%	mOS 41.6, 2 yr LCR 87.5	8	Bezjak [24]
			2.9%	2 yr LCR 90%, 2 yr OS 63.2%	24	*Chaudhuri [25]
			7.7% late toxicity	mOS 42.1, 3 yr LCR 95%	65	§Arnett [26]
50/4	112.5	258.3	2.9%	2 yr LCR 90%, 2 yr OS 63.2%	10	*Chaudhuri [25]
			11%	2 yr LCR 100%	47	#Rowe [27]
			1.2%	mOS 55.6 months, 3 yr LCR 96.5%	82	Chang [28]
48/4	105.6	240	<14.7%	mOS 42.1, 3 yr LCR 95%	34	§Arnett [26]
60/4	150	360	41% acute toxicity	Crude LCR 5.8%, 2year OS 52%	17	Bral [29]
60/3	180	460	27.3%	mOS 24.4 months	22	Fakiris [30]

*includes 7 ultracentral patients

[#]Includes metastases, mixed cohort with median dose and fractionation 50/4

[§] treated on consecutive days

mOS: median overall survival, LCR: Local control rate

Limitations

- There is no evidence to support one dose fractionation regime being superior in terms of efficacy or safety

Practical Considerations

- The dose constraints set out in RTOG 0813 are recommended (Tables 5-8)

Table 6. Conformality of Prescribed Dose for Calculations Based on Deposition of Photon Beam Energy in Heterogeneous Tissue for 50Gy in 5 fraction regime (from RTOG 0813)

PTV Volume (cc)	Ratio of Prescription Isodose Volume to PTV		Ratio of 50% Prescription Isodose Volume to PTV, R50%		Maximum Dose (% of dose prescribed) 2 cm from PTV in any direction, D2cm (Gy)		Percentage of Lung Receiving ≥20Gy, V20 (%)	
	Deviation		Deviation		Deviation		Deviation	
	None	Minor	None	Minor	None	Minor	None	Minor
1.8	<1.2	<1.5	<5.9	<7.5	<50.0	<57.0	<10	<15
3.8	<1.2	.<1.5	<5.5	<6.5	<50.0	<57.0	<10	<15
7.4	<1.2	<1.5	<5.1	<6.0	<50.0	<58.0	<10	<15
13.2	<1.2	<1.5	<4.7	<5.8	<50.0	<58.0	<10	<15
22.0	<1.2	<1.5	<4.5	<5.5	<54.0	<63.0	<10	<15
34.0	<1.2	<1.5	<4.3	<5.3	<58.0	<68.0	<10	<15
50.0	<1.2	<1.5	<4.0	<5.0	<62.0	<77.0	<10	<15
70.0	<1.2	<1.5	<3.5	<4.8	<66.0	<86.0	<10	<15
95.0	<1.2	<1.5	<3.3	<4.4	<70.0	<89.0	<10	<15
126.0	<1.2	<1.5	<3.1	<4.0	<73.0	>91.0	<10	<15
163.0	<1.2	<1.5	<2.9	<3.7	<77.0	>94.0	<10	<15

PTV: planning target volume

Table 7. Maximum dose limits to a point or volume within several critical organs. These are absolute limits, and treatment delivery that exceeds these limits will constitute a major protocol violation (from RTOG 0813)

Serial Tissue	Volume (cc)	Volume Max (Gy)	Max Point Dose (Gy)	Avoidance Endpoint
Spinal Cord	<0.25 <0.5	22.5 (4.5 Gy/fx) 13.5 (2.7 Gy/fx)	30 (6 Gy/fx)	Myelitis
Ipsilateral Brachial Plexus	<3	30 (6 Gy/fx)	32 (6.4 Gy/fx)	Neuropathy
Skin	<10	30 (6 Gy/fx)	32 (6.4 Gy/fx)	Ulceration
Parallel Tissue	**Critical Volume**	**Critical Volume Dose Max (Gy)**		**Avoidance Endpoint**
Lung (Right & Left)	1500	12.5 (2.5 Gy/fx)		Basic Lung Function
Lung (Right & Left)	1000	13.5 (2.7 Gy/fx)		Pneumonitis

Fx: fractions

Table 8. Suggested volume limits are listed for these organs to be used for treatment planning purposes. Since the tumour and normal tissue may not allow strict avoidance, the volume limits (columns 2 and 3) will not be scored as protocol violations if exceeded. However, the maximum point dose limits (column 4) must be respected (from RTOG 0813)

Serial Tissue*	Volume	Volume Max (Gy)	Max Point Dose (Gy)	Avoidance Endpoint
Esophagus, non-adjacent wall	<5 cc	27.5 Gy (5.5 Gy/fx)	105% of PTV prescription	Stenosis/fistula
Heart/Pericardium	<15 cc	32 Gy (6.4 Gy/fx)	105% of PTV prescription	Pericarditis
Great vessels, non-adjacent wall	<10 cc	47 Gy (9.4 Gy/fx)	105% of PTV prescription	Aneurysm
Trachea and ipsilateral bronchus, non-adjacent wall	<4 cc	18 Gy (3.6 Gy/fx)	105% of PTV prescription	Stenosis/fistula

Fx: fractions, PTV: Planning Target Volume

4. SABR for tumours >5cm

Advice

- Tumours >5cm in diameter can be treated with caution, provided that the OAR constraints for tumours <5cm can be met

Evidence

SABR is currently recommended for T1-2 tumours (or T3 tumours by virtue of invading chest wall) with a maximum size of 5cm [18]. Clinical trials have predominately excluded lesions larger than 5cm and therefore conventional fractionation schedules have been favoured in this group. Woody et al reported on 40 patients with a median tumour size of 5.6cm (range: 5.1-10cm) treated to a median dose of 50Gy in 5 fractions [31]. The 18-month local control rates and OS rate were 91.2% and 59.7% respectively. The grade 3 or higher toxicity rate was 7.5% which is comparable to other series. The normal tissue constraints used were the same as those for tumours ≤5cm as previously described [32]. A Dutch series reported on 63 patients with a median diameter of 5.8cm (range: 5.1-10.1) with a longer median follow up of 54.7 months [33]. They reported a median OS of 28.3 months, 2-year local control rates of 95.8% and out-of-field distant recurrence rate of 10%. It should be noted that 30% developed grade≥3 toxicity (radiation pneumonitis was the most common toxicity) and 19% of deaths were treatment-related (possibly related to undiagnosed interstitial lung disease in this cohort).

Limitations

- There is no prospective data to support SABR for tumours >5cm

Practical Considerations

- Dose constraints to OARs must be met as when treating lesions ≤5cm.
- Following treatment, patients should closely followed-up to detect and manage toxicity and expected higher distant relapse rates

5. Hypofractionation for central/ultra-central early-stage tumours not suitable for SABR

Advice

- Consider 50-60 Gy in 15 fractions in patients with central/ultra-central early stage NSCLC not suitable for SABR based on OAR constraints

Evidence

A prospective phase 1 dose escalation trial for patients of PS ≥2 with stage ≥II NSCLC not suitable for surgery, SABR or chemoradiation used increasing doses in 15 fractions (50 Gy, 55 Gy or 60Gy) to validate OAR constraints for a 15-fraction schedule in the IMRT/IGRT era with acceptable toxicities and no dose-limiting toxicity documented [34]. The subsequent randomised phase 3 study comparing 60 Gy in either 15 or 30 fractions in patients with ≥ PS 2 stage II-III NSCLC has published interim results in abstract form [35]. 60 patients had been enrolled (88% stage III), 28 treated with conventional fractionation, and 32 patients with 15 fractions. Chemotherapy was given to some patients sequentially (pre or post RT) but not concurrently. Less toxicity was reported in the 15-fraction arm, however, the complete trial, powered for OS with full toxicity rates, has not yet been published.

Cho et al [36] retrospectively reviewed hypofractionated RT for medically inoperable T1–T3 N0 NSCLC using a risk-adaptive dose schedule (60 Gy in 4, 15 or 20 fractions depending on location size and geometry of the tumour in relation to the oesophagus). 124 patients were included in the study; 72.6% had T1-2 N0 tumours; 65.3% had centrally located disease; 44.1% had PS 2-3; and 20.2% received 60Gy/15 fractions. In patients treated with 15 fractions, the rate of grade 3 pneumonitis was 4% with no grade 4 or 5 pneumonitis. The rate of grade 1 oesophagitis was 4% with no grade 2-5 oesophagitis.

Limitations

- OAR constraints for 15 fraction schedules were mostly derived from studies including patients with PS≥2 and stage II-III disease
- There are no prospective data to support 50-60 Gy in 15 fractions specifically in central or ultracentral early stage NSCLC

Practical Considerations

- Dose constraints to OARs for the 15 fraction schedule must be met with particular attention to the oesophageal constraint (Table 9; Stage 3 NSCLC section).

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Stage III NSCLC

1. Concurrent Chemoradiotherapy

Advice

- Consider for selected patients *
- Consider accelerated fractionation (i.e.55Gy/20 fractions)
- Limit chemotherapy dose **. Consider limiting chemotherapy to two cycles only and starting radiotherapy with cycle one.

Evidence

The randomised phase 2 'SOCCAR' trial [1] compared sequential versus concurrent chemotherapy combined with 55Gy in 20 fractions. The median number of cycles delivered was 2.8 in the concurrent arm. Toxicity was similar across both arms, with a median survival of 24 months (concurrent arm) in a UK population of patients with stage III NSCLC using 3D planning and treatment techniques. Following the study, a number of the participating centres adopted the schedule, fine-tuning chemotherapy regimens, evolving treatment techniques by applying PET-CT staging, 4D planning, IMRT and VMAT. With these adaptions, centres are reporting encouraging 58% 2-year survival [2] and acceptable rates of acute toxicity (including unpublished data from Glasgow), which compares favourably to more recent trials e.g. PACIFIC [3] where the 2-year survival was 55.6% in the standard arm.

Limitations

The evidence base for concurrent chemoradiotherapy using a hypofractionated accelerated fractionation schedule is limited, with the randomised trial evidence collected before many of the more modern staging and treatment techniques were in routine use. In addition, the SOCCAR trial only included 70 patients in the concurrent arm. The ability of retrospective audits of the UK post-trial experience to collect accurate toxicity data is limited, but centres indicate no significant toxicity signals even when treating larger PTVs e.g. >500cc ([2], personal communication).

Practical Considerations

*The constraints relating to the COVID-19 pandemic could limit mediastinal pathological staging and full respiratory assessment. Individual clinical judgments will need to be made in these circumstances. The inclusion criteria for the SOCCAR study can guide patient selection [1] i.e. pathologically confirmed stage III NSCLC, performance status 0 -1, with adequate hematological and biochemical reserve for chemotherapy treatment. It is advised that disease should be encompassed within a radical radiotherapy treatment where V20 is expected to be <30%, <12cm of oesophagus within PTV and that both FEV1 and transfer factor>50%. OARS constraints as per the SOCCAR protocol are detailed in Table 9.

** Chemotherapy as per SOCCAR protocol, concurrent phase: Vinorelbine: 15 mg/m^2 prior to radiotherapy fractions 1, 6, 15 and 20. Cisplatin: 20mg/m^2 with fractions 1-4 and 16-19 both IV. Adjuvant phase (2 cycles): Vinorelbine 25mg/m^2 days 1 & 8; Cisplatin 80mg/m^2 day 1. The median number of cycles actually delivered was 2.78. To limit chemotherapy exposure, consider omitting the adjuvant cycles and giving the concurrent chemotherapy cycles only, with cisplatin 60mg/m^2 IV or carboplatin AUC5 D1 and oral Vinorelbine 40mg/m^2 D1 and 8.

2. Radical radiotherapy +/- sequential chemotherapy

Advice

- Consider for selected patients
- Offer accelerated fractionation (55Gy/20 fractions)
- Consider further hypofractionation to 15 fractions*
- If offered, limit chemotherapy to 2 cycles, and consider giving adjuvantly following radiotherapy**

Evidence

The hypofractionated regimen of 55 Gy/20 fractions has been widely used in the UK [4], with audit data showing similar outcomes to CHART, 99% of patients completing treatment and 7% grade ≥3 toxicity rate [5].

Retrospective data using 45Gy in 15 fractions over 3 weeks (BED_{10} 58.5Gy) showed comparable outcomes to conventionally fractionated ≥60Gy [6]. However, radiobiological calculation suggests this schedule would not be isoeffective in comparison to 55Gy/20 fractions (BED_{10} 70.1Gy).

A higher dose hypofractionated regime (60Gy/15 fractions, BED_{10} 90Gy) has been reported by Sunnybrook in patients with stage I-III NSCLC [7]. 47 patients (52.8%) had stage II-III disease and the 2-year survival was 68% for this group. Importantly, the dose constraints derived for this study correspond well to those generated by Fenwick et al [8] using conversion from the I-START 20-fraction schedule (Table 9).

Dose escalation response analysis suggests there is an improvement in overall survival of 1-2% per Gy, and Nix et al [9] suggest that the survival gains are present when radiotherapy is the only treatment modality used. Hence the 4% absolute survival loss due to omitting sequential chemotherapy [10] could be countered by escalating between 2-4Gy EQD2 [9]. For a 20-fraction schedule this requires an additional 2.5Gy, and for the 15-fraction schedule that means escalating the physical dose by 2Gy.

Limitations

15-fraction schedules have generally been used to treat central early-stage disease, with the treatment of stage III patients limited to selected patients in some series [7]. It should be noted that the toxicity of this regime has not been reported specifically for patients with stage II-III.

Practical considerations

*These calculations suggest that if centres employ a 15-fraction schedule, doses in the 50–58Gy range can be considered.

Concerns over hypofractionated dose-escalated radiotherapy in NSCLC are dominated by late radiation toxicity involving central and perihilar structures [11]. The experience of accelerated schedules led to a UK research strategy that tested 4 separate escalation protocols in phase 1/2 studies. Two of these protocols used once daily hypofractionated schedules (IDEAL-CRT, I-START) with reassuring toxicity profiles [12, 13]. Applying the principles that Fenwick et al [8] used to develop these schedules to a 15-fraction schedule delivered over 19 – 21 days:

- Using an α/β of 10, 52Gy/15fractions is the isoeffective dose for tumour control and using an α/β of 3, 50Gy/15 fractions is isotoxic to 55Gy/20 fractions for late complications
- 58Gy/15 fractions would be the equivalent of the highest dose cohorts in these two studies (IDEAL-CRT 73Gy/30 fractions over 6 weeks, I-START 65Gy/20 fractions over 4 weeks).

The use of IMRT/VMAT is strongly recommended and centres without experience of dose escalation should take particular care that relevant normal tissues are accurately outlined and that their dosimetry is accurate. The radiotherapy planning guidelines for current stage III studies [14] are a resource that can help guide patient selection, outlining and planning using the modified dose constraints in Table 9.

** The addition of chemotherapy in the sequential setting will need careful consideration balancing a 4% absolute OS benefit over RT alone [10] against the additional infective risk posed by COVID-19. Consider giving RT first with deferred chemotherapy given when the risks related to COVID-19 start decreasing.

Table 9. Dose constraints for hypofractionated radiotherapy in Stage 3 NSCLC

Dose (Gy)	Volume	Concurrent CTRT 55Gy/20fx	RT only UK * 50 – 58Gy/15fx	RT only Canadian ** 50 – 60Gy/15fx
Spinal Cord	Max D 0.1cc	44Gy	<42Gy	38Gy
Oesophagus*	Max Vol	D 1cc <55Gy	D1cc <52Gy	50Gy V45 <10cc
Brachial Plexus	Max Vol	55Gy	<50Gy 0.5cc <42Gy	<50Gy
Heart/Pericardium	D100% D67% D33%	V_{30} <36%	<33Gy <40Gy <52Gy	Max 63Gy V57 <10cc
Mediastinal envelope	Max Vol		58Gy	(Great Vessels) 63Gy V57 <10cc
Trachea and Large Bronchus	Max Vol		58Gy	63Gy V57 <10cc
Rib	Max Vol			63Gy V30 <30cc
Skin	Max			0Gy
Stomach	Max Vol			50Gy V45 <10cc
Lung – GTV		V20 <35% MLD <18Gy	V19<35% MLD <16Gy	V20 <30% V5 <60% MLD <20Gy
Contralateral lung	V5		<60%	

*15 fraction conversion from the I-START 20 fraction schedule [13]
** Constraints based on Sunnybrook study [7] and clinical update via personal communication with Dr Patrick Cheung
MLD-mean lung dose; GTV: Gross Tumour Volume, CTRT: chemo-radiotherapy; fx: fractions

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Small cell lung cancer

1. Early-stage SCLC

Advice

- Consider SABR (with or without chemotherapy) in T1-2 N0M0 patients as an alternative to surgery or fractionated radiotherapy. Dose/fractionation and OAR constraints should be the same as those used for early-stage NSCLC.

Evidence

SABR is standard of care in medically inoperable early-stage NSCLC and is increasingly being delivered for early-stage SCLC [1-4]. SABR for early-stage SCLC is a treatment option in the ASTRO 2020 guidelines [5] and in the 2020 NCCN guidelines [6].

The largest series of SABR for LS-SCLC is a retrospective multicentre study including 74 patients [2]. It should be noted that only 59% of the patients received chemotherapy, 23% received PCI and >30% of patients had a performance status ECOG 2-3. Toxicity was mild with 5.2% grade ≥2 pneumonitis. Local progression-free survival was 96.1% and overall survival was 34% at 3 years.

Limitations

- Evidence base for SABR is limited to the peripheral early-stage SCLC setting. The risk of toxicity and development of lymph node metastases for central/ultra-central tumours is higher compared to peripheral tumours [7, 8]. As data is lacking in ultra-central early-stage SCLC, conventionally fractionated RT is more appropriate for these patients.

- The risk for lymph node metastases may be even higher with central/ultracentral versus peripheral lesions. Adapted hypofractionation (e.g. 60 Gy in 8 fractions or 50 Gy in 5 fractions) could be considered in selected early-stage central SCLC patients [7]. Given that data is lacking in ultracentral early-stage SCLC conventionally fractionated RT is more appropriate for these patients

- Given the risk of distant metastases, chemotherapy is generally considered in this setting for those patients who are suitable [1, 4]

Practical considerations

- When treating early-stage SCLC with SABR, dose/fractionation and OAR constraints should be the same as those used for early-stage NSCLC. 4DCT planning and daily cone-beam CT are mandatory.

- In patients who are suitable for chemotherapy, it is advisable to incorporate SABR early in the treatment course as the tumour volume may decrease significantly after the first or second cycle of chemotherapy and become difficult to visualize on image-guidance. SABR can be delivered before chemotherapy or between early cycles of chemotherapy. However, in the context of the COVID-19 pandemic the risk-benefit ratio of giving chemotherapy should be considered carefully

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2. Radiotherapy Fractionation in Good Performance Status Limited-Stage (LS) SCLC Patients

Advice:

- Consider 40Gy in 15 daily fractions with cycle 1 or 2 of chemotherapy in patients with good PS LS-SCLC.
- Consider 40Gy in 15 daily fractions after induction chemotherapy in patients who are not suitable for concurrent treatment.

- Limit chemotherapy to a maximum of four cycles

Evidence:

The current standard of care of early twice-daily radiotherapy (45Gy in 30 fractions) delivered concurrently with cycle 1 or 2 chemotherapy [1, 2]. This is reflected in the current 2019 NICE Lung Cancer guidelines [3]. However, the RCR Lung Cancer Consensus highlighted that hypofractionated regimes are currently used in the NHS and include 40Gy in 15 fractions, 50-55Gy in 20 fractions and 50Gy in 25 fractions (document in preparation).

A randomised study by NCIC (13) demonstrated a survival benefit with early concurrent radiotherapy (week 1) versus late (week 15) using 40Gy in 15 fractions (daily) in both arms [4]. Toxicity in both arms was acceptable. Severe neutropenia (<0.5 x 10^9/l) was common; infections requiring hospitalization occurred in< 5%. Severe lung toxicity was uncommon, with <3% pneumonitis in both arms.

Grønberg et al [5] reported a randomised phase 2 trial of 157 patients with LS- SCLC treated with 42Gy in 15 fractions once daily (OD) or 45Gy in 30 fractions twice daily (BD). There was no difference in one-year or median progression-free survival. Medial overall survival was longer with BD fractionation (6.3 months, p=0.61); There was no differences in ≥grade 3 oesophagitis (OD:31%, BD: 33%, p=0.80) or pneumonitis (OD: 2%, BD: 3%, p=1.0) (16).

Videtic et al [6] retrospectively reviewed 122 LS-SCLC patients who received concurrent chemotherapy with 50Gy in 25 fractions over 5 weeks (92pts) or 40Gy in 15 fractions over 3 weeks. There was no difference in treatment-related toxicity, overall survival and thoracic local control.

Xia et al [7] reported results on 59 LS- SCLC patients treated with 55Gy in 22 fractions over 30 days and concurrent chemotherapy. 25% of patients developed ≥grade 3 oesophagitis and 10% of patients developed ≥ grade 3 pneumonitis.

40Gy in 15 fractions has been used concurrently and sequentially in Leeds for limited stage SCLC for >10 years. Institutional dose constraints are listed below and a recent unpublished audit of 43 LD-SCLC patients treated with concurrent chemoradiotherapy 40Gy in 15 fractions showed a 1-year OS of 88% and a median OS of 26.9 months [15.6-50.4].

Limitations

- The initial data on 40Gy in 15 fractions is from 1993 (13) and therefore radiotherapy planning and delivery would be considered sub-optimal as: 1) diagnostic staging would not have involved mediastinal staging and/or PET/CT; 2) CT planning was not

mandatory (mainly 2D planning with posterior cord shield) and no 4DCT was used; 3) IGRT would have been with external tattoos alone or MV portal imaging.

- Most data on hypofractionated regimes are from retrospective single-institution studies.
- A variety of different hypofractionated regimes are used in the published literature and in routine UK practice.

Practical considerations

- When treating limited-stage SCLC with hypofractionated radiotherapy, IV contrast (if not contraindicated for the patient), and 3DCT/IMRT planning with an offline IGRT protocol with volumetric imaging are considered the standard of care. If possible, 4DCT planning and daily online CBCT is highly recommended, particularly if OAR doses are close to tolerance.
- Leeds OAR constraints for 40Gy/15 fractions regime are listed below (Table 10).

Table 10. Leeds organs at risk constraints in LS-SCLC

Lung-GTV	Controlateral lung (not mandatory)	Spinal canal PRV	Heart	Oesophagus	Brachial plexus
V20 <30% (ideally); up to 35% (accepted); MLD <15Gy (ideally); up to 18Gy (accepted)*	V20 <10% V10 < 50% V5 <70% MLD <8Gy	Max 36Gy D0.5cc <35Gy	D100%< 33%	Ideally, <12 cm should receive prescribed dose	D0.5cc <42Gy

- Constraints based on practice in Leeds, via personal communication with Dr Kevin Franks and Dr Mike Snee
- ***** A MLD (mean lung dose) of 18-20Gy and V20 of 35-40% can be considered in very selected cases
- ****** A margin of 5mm should be used to create a spinal cord PRV. A smaller margin may be used (e.g. 3mm) if the tumour is close to cord provided daily on-line imaging is requested and the cone beam CT is matched to bone

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Summary

This guidance document on reduced fractionation for lung cancer being treated with curative intent during the COVID-19 pandemic builds on a long tradition of hypofractionated radiotherapy in the UK. It reflects the current published literature and the combined experience of the authors and their colleagues in the UK and globally. However, it is acknowledged that for many centres, the fractionation regimens outlined will represent a significant change to current practice and standard of care. The extent of adoption of this guidance may reflect geographical pressures, although it is likely that all radiotherapy departments will need to adapt during this global pandemic.

This guidance document should be discussed with other specialist lung MDT members (e.g. thoracic surgeons and respiratory physicians) to disseminate the potential changes to practice that could be made in order to alleviate pressure on other departments (such as the need for post-operative high-dependency care beds).

Adequate discussion with the patient about the risk and benefits of treatment during the COVID-19 pandemic and uncertainties about toxicity from reduced fractionation where there is limited experience in a department are an essential component of the consent process.

The access to adequate nodal staging procedures (e.g. EBUS-TBNA) and respiratory function testing is likely to be compromised during the peak of the virus pandemic. Centres should document deviations from standard pre-treatment work-up as well as deviations from standard of care treatments. We strongly encourage prospective documentation of acute and late toxicities from reduced fractionation regimens and collection of outcome data to permit a multi-centre audit. We also urge colleagues to join national/international data collection initiatives on the impact of the COVID pandemic.

Additional information - international recommendations

Guckenberger M , et al.Practice recommendations for lung cancer radiotherapy during the COVID-19 pandemic: An ESTRO- ASTRO consensus statement. Radiother Oncol. 2020 S0167-140(20)30182-1 https://www.thegreenjournal.com/article/S0167-8140(20)30182-1/pdf

This joint ESTRO-ASTRO practice recommendation established pragmatic and balanced consensus recommendations in common clinical scenarios of radiotherapy for lung cancer in order to address the challenges of the COVID-19 pandemic.