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. This situation is resulting in unprecedented demands on the NHS as a whole posing a major burden on cancer services in the UK.

Approximately 49,000 new patients are diagnosed with lung cancer each year in the UK and >50% require radiotherapy treatment. The lung cancer population requiring active treatment has been classified as 'extremely vulnerable' with a significant proportion of previously treated lung cancer patients included in this category due to co-existing severe co-morbidities [1, 2]. There is therefore a need to mitigate the risks of their anti-cancer treatments by addressing risks associated with multiple visits to hospital, treatment-induced immune suppression, and radiation-associated lung injury. This means adapting our current treatment protocols rapidly to reflect the shifting risk-benefit ratio and diminished resources. Furthermore, 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 due to the deferral of radiotherapy for disease sites such as breast and prostate.

General guidance on delivery of radiotherapy during the COVID-19 pandemic has been provided by NICE [3]. One recommendation is to consider alternative dose-fractionation schedules or radiotherapy techniques.

The objectives of this paper are: to identify reduced-fractionation and curative-intent radiotherapy regimes in lung cancer, assess their evidence base, and provide organs-at-risk (OAR) dose constraints. We also discuss limitations and practical considerations associated with the implementation of these reduced-fractionation regimes. The anticipated impact of this work is firstly, to reduce hospital visits and limit exposure to COVID-19 in patients having curative-intent radiotherapy for lung cancer, and secondly, 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.

Methods

Systematic reviews and relevant papers were identified by a group of UK clinical oncologists through a PubMed search between 20/3/2020 and 30/3/2020. We also included published and unpublished audits of hypofractionated regimes from UK centres.

Early stage NSCLC

UK practice is based on the recommendations from the UK SABR consortium (18). Here we outline the evidence for reduction in SABR fraction number and provide OAR dose constraints from existing international protocols. We also outline the evidence for hypofractionation (beyond 55Gy in 20 fractions) for central/ultra-central 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 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 [4].

Evidence

Single-fraction schedules of 30-34Gy have been compared to multi-fraction SABR in two phase 2 studies (RTOG 0915, Roswell Park) [5-7]. 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 [8]. 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 numbers treated within 2 cm 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 move 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; online appendix).

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

Advice

- Consider 3-fraction regimes (e.g. 54Gy/3 fractions).
- Where the planning target volume (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% [9]. 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) [10-13]. Multi-fraction retrospective data specifically looking at patients with tumours near the chest wall are shown in Table 3 (online appendix). 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) [12]. Where the PTV is abutting the chest wall, data from Andolino et al suggests 48Gy/3 fractions has a lower toxicity than 54Gy/3 fractions [10].

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; online appendix).

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 2cm of the bronchial tree, trachea, major vessels, oesophagus, heart, pericardium, or brachial plexus, or a PTV abutting mediastinal pleura or pericardium, excluding ultra-central disease. An ultra-central 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) [14].
- 8 fractions as per UK SABR consortium (total dose 60Gy) [15].

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 [16]. 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; online appendix). 50Gy/4 fractions has also been used in North America but lacks prospective trial data and dose constraints.

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 6-8; online appendix).

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 [15]. Clinical trials have predominantly 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 with a median dose of 50Gy in 5 fractions [17]. The 18-month local control, OS and grade 3 toxicity rates rate were 91.2%, 59.7% and 7.5% respectively. 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 [18]. The median OS, 2-year local control and out-of-field distant recurrence rates were 28.3 months, 95.8% and 10% respectively. 30% developed grade≥3 toxicity (radiation pneumonitis was the most common toxicity) and 19% of deaths were treatment-related.

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 50-60Gy 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 performance status (PS≥2) with stage ≥II NSCLC not suitable for surgery, SABR or chemoradiation used increasing doses in 15 fractions (50Gy, 55Gy or 60Gy) to validate OAR constraints for a 15 fraction schedule in the IMRT/IGRT era. They reported acceptable toxicities and no dose-limiting toxicity was documented [19]. The subsequent randomised phase 3 study comparing 60Gy in either 15 or 30 fractions in patients with PS≥2 stage II-III NSCLC has published interim results in abstract form [20]. 60 patients had been enrolled (88% stage III). Chemotherapy was given to some patients sequentially (pre or post RT) but not concurrently. Less toxicity was reported in the 15 fraction arm. Cho et al [21] retrospectively reviewed hypofractionated RT for medically inoperable T1–T3 N0 NSCLC using a risk-adaptive dose schedule (60Gy 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 4-5 pneumonitis and no grade 2-5 oesophagitis reported.

Limitations

- OAR constraints for 15-fraction schedules were mostly derived from studies including patients with PS≥2 and stage II-III disease.

- There is no prospective data to support 50-60Gy in 15 fractions specifically in central or ultra-central early stage NSCLC.

Practical Considerations

- Dose constraints to OARs for the 15-fraction schedule must be met with particular attention to the oesophageal constraint (see Table 9; online appendix).

Stage III NSCLC

1. Concurrent Chemoradiotherapy

Advice

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

Evidence

The randomised phase 2 SOCCAR trial [22] 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, and evolving treatment techniques by applying PET-CT staging, 4D planning, IMRT and VMAT. With these adaptions, UK centres are reporting encouraging 58% 2-year survival and acceptable rates of acute toxicity [23], which compares favourably to more recent trials, e.g. PACIFIC [24].

Limitations

The SOCCAR study only included 70 patients in the concurrent arm. It was published before many of the more modern staging and treatment techniques were in routine use. The evidence base for contemporary concurrent chemoradiotherapy using a hypofractionated accelerated fractionation schedule is therefore limited (particularly concerning acute and late toxicity) and of a retrospective nature [23].

Practical Considerations

- The inclusion criteria for the SOCCAR study can guide patient selection [22]. OARs constraints as per SOCCAR protocol are detailed in Table 9 (online appendix).
- Chemotherapy as per SOCCAR protocol [22] can be adapted during the COVID-19 epidemic. Consideration should be given to omitting the adjuvant cycles and delivering the concurrent chemotherapy cycles only (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 (see practical considerations below).
- Offer accelerated fractionation (55Gy/20 fractions).
- Consider further hypofractionation (50-58Gy in 15 fractions).
- If offered, limit chemotherapy to 2 cycles and consider delivering it following radiotherapy (see practical considerations below).

Evidence

The hypofractionated regimen of 55Gy/20 fractions has been widely used in the UK [25], with audit data showing similar outcomes to CHART, 99% of patients completing treatment, and a 7% grade ≥3 toxicity rate [26]. Retrospective data on 45Gy in 15 fractions over 3 weeks (BED_{10} 58.5Gy) showed comparable outcomes to doses ≥60Gy given with conventional fractionation [27]. 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 of 60Gy/15 fractions (BED_{10} 90Gy) has been reported by Sunnybrook in patients with stage I-III NSCLC [28]. 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 using conversion from the I-START 20 fraction schedule [29] (Table 9; online appendix).

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 [28]. It should be noted that the toxicity of this regime has not been reported specifically for patients with stage II-III.

Practical considerations

- Concerns over hypofractionated dose-escalated radiotherapy in NSCLC are dominated by late radiation toxicity involving central and perihilar structures [30]. 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 [31, 32]. Applying the principles that Fenwick et al [29] used to develop these schedules to a 15-fraction schedule delivered over 19 – 21 days:
    - Using an α/β of 10, 52Gy/15 fractions 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. The radiotherapy planning guidelines for current stage III studies [33] are a resource that can help guide patient selection, outlining and planning using the modified dose constraints in Table 9 (online appendix).

- The addition of chemotherapy in the sequential setting will need careful consideration, balancing a 4% absolute OS benefit over RT alone [34] against the additional infective risk posed by COVID-19. Consideration should be given to RT first, with deferred chemotherapy given later when the risks related to COVID-19 start decreasing.

Small cell lung cancer

1. Early-stage SCLC

Advice

- Consider SABR (with or without chemotherapy) in T1-2 N0 M0 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 [35-38]. SABR for early-stage SCLC is a treatment option in the ASTRO 2020 guidelines [39] and in the 2020 NCCN guidelines [40].

The largest series of SABR for LS-SCLC is a retrospective multicentre study including 74 patients [38], of which only 59% of the patients received chemotherapy, 23% received PCI and >30% of patients had a PS 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 [41,42]. As data is lacking in ultra-central 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 [35, 38].

Practical considerations

- In the context of the COVID-19 pandemic, the risk-benefit ratio of giving chemotherapy should be considered carefully. In patients who are suitable for chemotherapy, it is advisable to give SABR first as the tumour volume may decrease significantly after the first or second cycle of chemotherapy and become difficult to visualize on image-guidance.

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

Advice

- Consider 40Gy in 15 daily fractions given with 1st or 2nd cycle 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 is twice-daily radiotherapy (45Gy in 30 fractions) delivered concurrently with cycle 1 or 2 chemotherapy [43-45]. However hypofractionated regimes are also used in UK centres and include: 40Gy in 15 fractions and 50-55Gy in 20 fractions. A randomised study by NCIC demonstrated a survival benefit with early concurrent radiotherapy (week 1) versus late (week 15) using 40Gy in 15 daily fractions [46]. Toxicity in both arms was acceptable. Grade 4 neutropenia was

common and pneumonitis was <3%. Grønberg et al [47] 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. There were no differences in ≥grade 3 oesophagitis (OD: 31%, BD: 33%, p=0.80) or pneumonitis (OD: 2%, BD: 3%, p=1.0) [47]. Videtic et al [48] 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 [49] 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 in Table 10 (online appendix) and a recent unpublished audit of 43 LS-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 [46], and therefore radiotherapy planning and delivery would be considered sub-optimal.
- 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 LS-SCLC with hypofractionated radiotherapy, IV contrast (if not contraindicated), and 3DCT/IMRT planning with an offline IGRT protocol with volumetric imaging are considered the standard of care. 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 in Table 10 (online appendix).

Discussion

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 as 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. That discussion will disseminate the potential changes to radiotherapy practice that could be made in order to alleviate pressure on other departments such as thoracic surgery.

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.

Centres should document deviations from standard pre-treatment work-up as well as deviations from standard of care treatments. We consider prospective and multi-centre documentation of outcome (including toxicity) from these reduced fractionation regimens as essential. We also urge colleagues to join national/international data collection initiatives on the impact of the COVID-19 pandemic.

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Supplementary Materials

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

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	10	14
	<1.2	7	
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	

Table 3. Dose/fractionation, biological effective dose, 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 [1]	18	54/3 (median)	378	151	0.1	100% any grade
Andolino [1]	61	48/3	304	125	0.2	0% any grade
Asai[2]	116	48/4	240	106	2 (0.3 – 6.2)	24.1% rib fracture, 0.86% G3
Bongers [3]	183	60/3	460	180	<2.5 85.5%*	Any grade CWP: 10.4% G3 CWP: 1.6%
Bongers [3]	187	60/5	300	132	<2.5 91%*	Any grade CWP: 14.4% G3 CWP: 3.2%
Bongers [3]	73	60/8	210	105	<2.5 71.4%*	Any grade CWP: 15% G3 CWP: 1.4%
Nambu [4]	95	48/4	240	106	0.6 (0 - 5.3)	G3 CWP 0%
Nambu [4]	45	60/10	180	96	0.6 (0 - 5.3)	G3 CWP 0%
Nambu [4]	37	70/10	233.3	119	0.6 (0 - 5.3)	G3 CWP 0%

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

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

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 [1]	18	54/3	378	151	64	64	100% any grade, worst possible G3 rate 16.6%
Andolino [1]	61	48/3	304	125	57	52	0% any grade
Taremi [5]	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 [6]	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 [5]	46	54/3	378	151	D0.5cc 60 Gy	50% rib fracture
		60/3*	460	180		
Dunlap [7]	60	21-60/3-5 (60/3)	460	180	V30 (30cc)	G2 CWP 30% if V30>35cc
Mutter [8]	126	40-60/3-5 (54/3)	378	151	V30 (70cc)	G2 CWP 27.8% correlated with V30 >70cc
Stephans [9]	45	60/3	460	180	V30 <30cc	G2 CWP 10-15% if V30<30cc
Welsh [10]	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

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 [11]
			Unknown G3 rate, but 0% G4 toxicity	mOS, n/a, 4 yr LCR 77.8%*	9	Taremi [12]
			6.4%	mOS 38 months, LCR n/a	80	Tekatli [13]
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 [14]
			0%	mOS NR, LCR 100%	10	Olsen [15]
			0%	mOS 41.6, 2 yr LCR 87.5	8	Bezjak [16]
			2.9%	2 yr LCR 90%, 2 yr OS 63.2%	24	*Chaudhuri [17]
			7.7% late toxicity	mOS 42.1, 3 yr LCR 95%	65	§Arnett [18]
50/4	112.5	258.3	2.9%	2 yr LCR 90%, 2 yr OS 63.2%	10	*Chaudhuri [17]
			11%	2 yr LCR 100%	47	#Rowe [19]
			1.2%	mOS 55.6 months, 3 yr LCR 96.5%	82	Chang [20]
48/4	105.6	240	<14.7%	mOS 42.1, 3 yr LCR 95%	34	§Arnett [18]
60/4	150	360	41% acute toxicity	Crude LCR 5.8%, 2year OS 52%	17	Bral [21]
60/3	180	460	27.3%	mOS 24.4 months	22	Fakiris [22]

* Includes 7 ultracentral patients

Includes metastases, mixed cohort with median dose and fractionation 50 Gy/4 fx

§ Treated on consecutive days

mOS: median overall survival; LCR: local control rate

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

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 (23)

** Constraints based on Sunnybrook study (24) and clinical update via personal communication with Dr Patrick Cheung

MLD-mean lung dose; GTV: Gross Tumour Volume, CTRT: chemo-radiotherapy; fx: fractions

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 35Gy D0.5cc <36Gy	D100%<33 %	Ideally, <12 cm should receive total 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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Author contributions

1 guarantor of integrity of the entire study - CFF
2 study concepts and design - CFF
3 literature research – all authors
4 clinical studies – N/A
5 experimental studies / data analysis – N/A
6 statistical analysis – N/A
7 manuscript preparation – all authors
8 manuscript editing – all authors

***Declaration of Interest Statement**

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