Managing treatment gaps in radiotherapy of lung cancer during the COVID-19 pandemic

John D Fenwick[1,2], Corinne Faivre-Finn[3,4], Kevin N Franks[5,6] and Matthew QF Hatton[7]

[1]Institute of Translational Medicine, University of Liverpool

[2]Department of Physics, Clatterbridge Cancer Centre, Liverpool

[3]The Christie NHS Foundation Trust, Manchester

[4]The University of Manchester

[5]Leeds Cancer Centre

[6]University of Leeds

[7]Weston Park Hospital, Sheffield

Introduction

The *Guidance on management of unscheduled treatment interruptions* (2019) provided by The Royal College of Radiologists (RCR) classifies patients with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) as Category 1, for whom there is very strong evidence that radiotherapy prolongation adversely affects survival or local control rates. For these patients it is therefore important to mitigate effects of unplanned gaps in treatment. As noted in section 8.6 of '*COVID-19 rapid guideline: delivery of radiotherapy*' (NICE, 2020), during the COVID-19 pandemic this should continue to be done following the RCR guidance.

Here we suggest how this might be achieved for lung cancer treatments, according to the principles set out in the RCR's *Additional guidance on management of unscheduled treatment interruptions in patients during the COVID-19 pandemic* (2020). The advice provided is not prescriptive, and should be discussed within teams for local adoption.

Schedules delivering doses-per-fraction ≤ 4 Gy

Commonly, gaps in radiotherapy are offset by finishing courses faster, delivering some remaining fractions twice-per-day or at the weekend as described in section 5.2 of the RCR report. This is the most effective approach and should be used when possible (Hendry *et al*, 1996). During the pandemic, though, it may not be practical, in which case we suggest the following two-step framework, adapted from section 5.3 of the report –

i)   <u>Consider giving RT in shorter schedules</u> to make best use of NHS resources, reduce risk of infection, and decrease the chance of a treatment break becoming necessary, following the recommendation to use the shortest safe form of treatment made in section 8.7 of the NICE COVID-19 guidance. Details of suggested schedules can be found together with dose-limits in *Reduced fractionation in lung cancer patients treated with curative-intent radiotherapy during the COVID-19 epidemic* available at https://www.rcr.ac.uk/sites/ default/files/lung-cancer-radiotherapy-covid19.pdf

ii) <u>If a treatment break does occur, consider escalating dose</u> to the extent described below to offset the gap, either by <u>adding fractions to the schedule</u> or <u>using dose-per-fraction escalation</u>. Evaluate the feasibility of escalation by comparing resulting normal tissue doses with limits listed for suggested treatments, as also described below. Then choose whether to:

   a. escalate to the whole extent suggested;

   b. deliver the original planned dose accepting a reduction in effectiveness;

   c. escalate to an intermediate degree.

NSCLC: RT and sequential chemo-RT

For NSCLC, classical linear-quadratic (LQ) modelling uses a 10 Gy α/β ratio, and views accelerated repopulation as starting 28 days after initiation of RT and negating 0.6-0.8 Gy EQD2 per day of treatment extension (Mehta *et al,* 2001). Therefore, if a treatment gap extends the total RT duration beyond 28 days, consider increasing the tumour dose <u>by 0.75 Gy EQD2 (0.9 Gy BED) per day of additional schedule protraction beyond day 28</u>.

A reduction of 1 Gy EQD2 has been associated with a 1% absolute fall in 2-year overall survival (OS) for RT alone and sequential chemo-RT of NSCLC (Nix *et al* 2020), and a 2% fall in 2-year disease-free survival (Partridge *et al* 2011). Therefore, each day of RT protraction beyond 28 days might reduce the survival rate by around 0.75-1.5% if left uncompensated, similar to the 1.6% per day estimate of Fowler and Chappell (2000).

During the pandemic short <u>15- and 20-fraction schedules</u> are suggested, delivering 50-52 Gy over 19 days or 55 Gy over 26 days. If tumour dose is increased <u>using dose-per-fraction escalation</u>, then the additional physical dose required to raise tumour EQD2s by each 0.75 Gy <u>is 0.54 Gy for the 15-fraction schedule, and 0.58 Gy for the 20-fraction schedule</u>. Thus, if T_e and T_o are the durations of the RT schedule with and without the gap, consider escalating the prescribed dose by

   0.54 Gy $\times$ { Max[$T_e - 28{,}0$] – Max[$T_o - 28{,}0$] } for the 15-fraction schedule,

   0.58 Gy $\times$ { Max[$T_e - 28{,}0$] – Max[$T_o - 28{,}0$] } for the 20-fraction schedule

For the <u>15-fraction</u> schedule a <u>1-week gap</u> would extend treatment to 26 days, and require <u>no correction</u> since accelerated repopulation starts at 28 days. A <u>2-week gap</u> would extend the duration to 33 days, and could be offset via dose-per-fraction escalation, increasing the total prescribed dose given over all 15 fractions by $0.54\times(33-28) =$ <u>2.7 Gy</u>. For the <u>20-fraction schedule,</u> a <u>1-week gap</u> would extend treatment duration to 33 days, and could be offset by increasing the prescribed dose by $0.58\times(33-28) =$ <u>2.9 Gy</u>. Table 1 summarizes increases in prescribed dose required to compensate 1-, 2- and 3-week gaps in the 15- and 20-fraction schedules when dose-per-fraction escalation is used.

<u>We suggest limiting escalation of prescribed doses delivered by the 15-and 20-fraction schedules respectively to $\leq$58 Gy and $\leq$65 Gy respectively.</u> In the UK ISTART trial of 20-fraction RT, 65 Gy was the highest prescribed dose-level tested. While initial trial data indicate that toxicity was acceptable overall (Lester *et al* 2018), full results including the number of patients receiving 65 Gy have yet to be published. <u>The 61 Gy oesophageal dose-</u>

limit listed for this schedule in Table 2 was found safe in 12 ISTART patients, and we suggest paying particular attention to this limit.

Table 1. Additional physical doses needed to correct 1-, 2- and 3-week gaps in the 15- and 20-fraction schedules for NSCLC using dose-per-fraction escalation.

Gap	15-fraction schedule	20-fraction schedule
1-week gap	0	2.9 Gy
2-week gap	2.7 Gy	7.0 Gy
3-week gap	6.5 Gy	11.0 Gy $\rightarrow$ 10 Gy*

* 11.0 Gy is required to offset the 3-week gap, but we suggest not escalating this schedule by more than 10 Gy.

Consider whether to use dose-per-fraction escalation, or to increase dose by delivering additional fractions. The unmodified 15-fraction schedule delivers 50-52 Gy in 3.33-3.47 Gy/fraction, and an additional fraction in this range is worth an extra 3.7-3.9 Gy EQD2, equivalent to 5 days' gap correction. Similarly, the unmodified 20-fraction schedule delivers 55 Gy in 2.75 Gy/fraction, and each added fraction of this size is worth an extra 2.9 Gy EQD2 or 4 days' gap correction.

If you do add fractions, giving the same dose-per-fraction as in the pre-gap treatment, you can directly compare values of normal tissue dose-metrics for plans summed over the pre- and post-gap phases with protocol dose-limits for the schedule originally being used, listed in the RCR '*Reduced fractionation*' document, and in Table 2 here. For example, if you have added two extra 3.33 Gy fractions to a 15-fraction schedule, you can compare totaled dose metrics with protocol limits for the 15-fraction schedule.

If you choose to use dose-per-fraction escalation, we suggest limiting doses-per-fraction to ≤4 Gy. For 15-fraction treatments, summed normal tissue dose-metrics can then still be compared with dose-limits protocolized for this schedule (Table 2). But for dose-per-fraction escalated 20-fraction treatments, we suggest you carry out linear-quadratic (LQ) calculations when comparing proposed treatments with 20-fraction schedule protocol dose-limits, to account for changes in dose-per-fraction over the course of the modified treatment. If you do directly compare summed dose-volume metrics with 20-fraction protocol limits, though, you should first reduce those limits by 1.6 Gy. You may wish to carry out LQ calculations for the 15-fraction schedule too. Details are provided in the appendix.

You might both increase the size of remaining scheduled fractions and also add extra fractions to the same treatment. In this case we suggest carrying out LQ calculations to assess the tumour effect, as described in the Appendix. Normal tissue safety can be checked as described above, provided you remain within the limits suggested on total dose and dose-per-fraction.

NSCLC: concurrent chemo-RT

For concurrent chemoradiotherapy treatments, McMillan *et al* (2017) demonstrated a significant reduction in overall survival with treatment protraction due to unscheduled gaps: 2-year OS was 9% lower for treatments with 5-9 day gaps compared to treatments with no gaps, a fall of 1.3% per day of protraction. Debate continues over whether OS can be increased by escalating doses beyond 63 Gy EQD2, a meta-analysis of Ramroth *et al* (2016) reporting *lower* survival in escalated treatments, reflecting results from RTOG-0617 (Bradley 2016). In any case, escalation might be more effective at compensating for tumour repopulation during gaps than at increasing cell-kill beyond an already high level. And an analysis of Nix *et al* (2020) indicates that 2-year OS rises by around 1.5% per Gy as prescribed EQD2 is increased from 50 to 60 Gy. We therefore suggest correcting gaps by <u>adding 0.75 Gy EQD2 per day of additional RT schedule protraction beyond day 28.</u>

Table 2. Normal tissue dose constraints for moderately hypo-fractionated radiotherapy in stage 3 NSCLC.

Structure	Concurrent CRT 55Gy/20fx[*]	RT ± seq chemo 55Gy/20fx[**]	RT ± seq chemo UK 50-58Gy/15fx[†]	RT ± seq chemo Can 50-60Gy/15fx[††]
Spinal cord	D_{max} <44 Gy	$D_{0.1cc}$ <47 Gy	$D_{0.1cc}$ <42 Gy	D_{max} <38 Gy
Oesophagus*	D_{1cc} <55 Gy	D_{1cc} <61 Gy	D_{1cc} <52 Gy	D_{max} <50 Gy V_{45Gy} <10 cc
Brachial plexus	D_{max} <55 Gy	$D_{0.1cc}$ ≤ 55 Gy	D_{max} <50 Gy $D_{0.5cc}$ <42 Gy	D_{max} <50 Gy
Heart/ Pericardium	V_{30Gy} <36%	$D_{100\%}$ <36 Gy $D_{67\%}$ <44 Gy $D_{33\%}$ <57 Gy	$D_{100\%}$ <33 Gy $D_{67\%}$ <40 Gy $D_{33\%}$ <52 Gy	D_{max} <63 Gy V_{57Gy} <10 cc
Mediastinal envelope		D_{max} <65 Gy	D_{max} <58 Gy	(Great Vessels) D_{max} <63 Gy V_{57Gy} <10 cc
Trachea & large bronchus			D_{max} <58 Gy	D_{max} <63 Gy V_{57Gy} <10 cc
Rib				D_{max} <63 Gy V_{30Gy} <30 cc
Skin				D_{max} <50 Gy
Stomach				D_{max} <50 Gy V_{45Gy} <10cc
Lung – GTV	MLD <18 Gy V_{20Gy} <35%	MLD<17.2 Gy V_{20Gy} <35%	MLD <16 Gy V_{19Gy}<35%	MLD <20 Gy V_{20Gy} <30% V_{5Gy} <60%
Contralateral		V_{5Gy} <60%	V_{5Gy} <60%	

lung

CRT = chemoradiotherapy; RT = radiotherapy; seq chemo = sequential chemotherapy; $D_{X\%\ or\ cc}$ = dose to most highly irradiated X% or cc of structure; V_{XGy} = fractional structure volume receiving $\geq$ X Gy; MLD = mean (physical) lung dose.

[*] SOCCAR constraints. [**] ISTART/AdSCAN constraints (Lester *et al*).[†] Conversion to a 15-fraction schedule from the I-START 20-fraction schedule. [††] Constraints currently used in Sunnybrook, Toronto, study (Zeng *et al*, 2018), with clinical update via personal communication from Dr Patrick Cheung.

During the pandemic a 20-fraction schedule delivering a baseline 55 Gy in 26 days is suggested. If dose-per-fraction escalation is used to compensate gaps, 0.54 Gy physical dose should be added for each required 0.75 Gy EQD2 increase. Thus prescribed dose should be increased by 0.54 Gy $\times$ { Max[$T_e - 28,0$] – Max[$T_o - 28,0$] }, where T_e and T_o are the durations of the RT schedule with and without the gap.

Resulting total additional doses for 1-, 2- and 3-week gaps are listed in Table 3. For this concurrent treatment, we suggest limiting the maximum prescribed dose to 63 Gy, a level with an EQD2 ($\alpha/\beta = 3$ Gy) just below that of the upper limit tested in the IDEAL-CRT trial of concurrent chemo-RT given in 30 radiation fractions. We also suggest limiting escalated doses-per-fraction to $\leq$3.5 Gy. Summed normal tissue dose-metrics can then be directly compared with the protocol dose-limits listed in the RCR '*Reduced fractionation*' guidance and Table 2 here. Alternatively, you may wish to carry out linear-quadratic (LQ) calculations as described in the Appendix.

Table 3. Additional physical doses needed to correct 1-, 2- and 3-week gaps in the 20-fraction concurrent chemo-RT treatment of NSCLC using dose-per-fraction escalation.

Gap	Additional physical dose
1-week gap	2.9 Gy
2-week gap	7.0 Gy
3-week gap	11.0 Gy $\rightarrow$ 8 Gy*

* Complete compensation of a 3-week gap would require an additional physical dose of 11 Gy,
but we suggest limiting this to 8 Gy, to avoid escalating prescribed dose beyond 63 Gy.

If you escalate by adding fractions, giving the same dose-per-fraction as in the pre-gap treatment, values of dose-metrics of plans summed over pre- and post-gap phases can be directly compared with unadjusted protocol dose-limits for the 20-fraction concurrent chemo-RT schedule. Each additional 2.75 Gy fraction is worth an extra 2.9 Gy tumour EQD2, equivalent to 4 days' gap correction.

SCLC

Sas-Korczynska *et al* (2013) reported a fall in 5-year OS of 0.28% per day's extension of the total period between the start of chemotherapy and the end of RT. In data of Hasan *et al* (2018), schedules delivering 15 Gy greater physical dose were associated with 7% higher 3-year OS, an increase of 0.47% per Gy, although OS was not associated with differences in dose-per-fraction over the range 1.5-3.0 Gy. Combining this information, reduced survival due to gaps might be offset by adding 0.60 Gy physical dose per day of gap-length.

During the pandemic <u>a 15-fraction, 19-day schedule delivering 40 Gy in fractions of 2.67 Gy should be considered. We suggest correcting for gaps by adding dose to this treatment according to</u>

$$\underline{\text{Extra physical dose} \; = \; 0.60 \text{ Gy} \times \{ \text{Max}[T_e - 28, 0] - \text{Max}[T_o - 28, 0] \; \}}$$

where T_e and T_o are the durations of the RT schedule with and without gaps.

Consider, for example, 7-day and 14-day gaps which extend RT duration to 26 and 33 days. We suggest adding $0.6 \times 0 = 0$ Gy to compensate for the 7-day gap, and $0.6 \times 5 = 3.0$ Gy for the 14-day gap. The approach is summarized in Table 4. It corrects for accelerated repopulation in progress 28 days into RT (De Ruyscher *et al*, 2006) and running at 0.6 Gy per day.

Table 4. Additional physical doses needed to correct 1-, 2- and 3-week gaps in radiotherapy of SCLC.

Gap	Additional physical dose
1-week gap	0 Gy
2-week gap	3.0 Gy
3-week gap	7.2 Gy

<u>We do not suggest escalating the 15-fraction schedule beyond 58 Gy prescribed dose. Escalation can be achieved by adding fractions, checking feasibility by directly comparing dose-metrics of plans summed across pre- and post-gap phases with protocol dose-limits</u> listed in the RCR '*Reduced fractionation*' guidance and Table 5 here. <u>Or dose-per-fraction escalation can be used, in which case we suggest limiting doses-per fraction to ≤4 Gy for non-concurrent treatments, and ≤3.5 Gy for concurrent CRT.</u>

Table 5. Normal tissue dose limits for 40Gy/15 fraction SCLC regimen (Leeds practice, personal communication from Drs Kevin Franks and Mike Snee).

Structure	Limit
Spinal canal PRV*	D_{max} <36 Gy, $D_{0.5cc}$ <35 Gy
Oesophagus	≤12 cm length to receive prescribed dose
Brachial plexus	$D_{0.5cc}$ <42 Gy

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to ensure you have the latest version. This document is the collaborative work of oncologists and their teams, and is not a
formal RCR guideline or consensus statement.

Heart	$D_{33\%}$ < prescribed dose
Lung – GTV	MLD <15 Gy ideally, though 18 Gy accepted V_{20Gy} < 30% ideally, though 35% accepted
Contralateral lung (not mandatory)	MLD <8 Gy, V_{20Gy} <10%, V_{10Gy}<50%, V_{5Gy}<70%

PRV = planning risk volume; $D_{X\% \text{ or cc}}$ = dose to most highly irradiated X% or cc of structure; V_{XGy} = fractional structure volume receiving $\geq$ X Gy; MLD = mean (physical) lung dose.

*A margin of 5 mm 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.

** An MLD of 18-20Gy and V_{20Gy} of 35-40% can be considered in very selected cases.

You may wish to carry out LQ calculations when comparing dose-per-fraction escalated treatments with protocol limits on normal tissue doses for the 15-fraction SCLC schedule. <u>If you directly compare dose-metrics from summed plans with these protocol limits, you should first reduce the limits by 1.3 Gy.</u> The Appendix provides further details.

SABR schedules

SABR schedules are usually delivered within 3 weeks (van Baardwijk *et al* 2012) and commonly within 1-2 weeks (Loganadane *et al* 2016), and mean reported durations range from 4 days to 4 weeks. Variation of outcome with duration is not yet well characterized. While an overall duration <10 days is associated with better local control, this might simply be because shorter, more hypo-fractionated courses deliver higher biologically effective doses (Loganadane *et al* 2016). For a 5-fraction SABR schedule, a non-significant trend towards superior local control was found for treatments given on alternate days rather than daily (Alite *et al* 2016), perhaps because of the longer time available for tumour re-oxygenation. Taking these factors into account, we suggest –

1. <u>Initially plan to complete SABR schedules in as short a time-frame as possible, while leaving 48 hour intervals between fractions</u>, short treatments minimizing the risk of gaps occurring, and allowing rapid completion after a break. Suggested schedules can be found in '*Reduced fractionation in lung cancer patients treated with curative-intent radiotherapy during the Covid-19 epidemic*' available at https://www.rcr.ac.uk/sites/default/files/lung-cancer-radiotherapy-covid19.pdf.

2. <u>Should a break in treatment occur, complete SABR delivery as rapidly as possible subject to 48 hour minimum intervals between fractions</u>, as described in section 5.5 of the RCR guidance.

Protraction of schedule duration beyond 4 weeks raises the question of whether to escalate the dose. We do not suggest this, since the required degree of escalation is presently unknown. Overall, <u>make every effort to complete a SABR treatment within four weeks</u>.

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Appendix

1. LQ calculations to check tumour EQD2 for NSCLC

We suggest using an α/β ratio of 10 Gy for NSCLC (Mehta *et al* 2001). Accordingly, baseline EQD2s for the two proposed NSCLC schedules are –

EQD2$_{\text{baseline}}$ = 55.6-58.4 Gy for 15 × 3.33-3.47 Gy/fx and 58.4 Gy for 20 × 2.75 Gy/fx

Determine how much EQD2 you need to add to offset a treatment gap

$$\Delta\text{EQD2} = 0.75\,\text{Gy} \times \text{Max}[T - 28, 0]$$
(1)

where *T* is the duration (days) of radiotherapy including the gap. Then calculate the total tumour EQD2 you would ideally deliver

$$\text{EQD2}_{\text{target}} = \text{EQD2}_{\text{baseline}} + \Delta\text{EQD2}$$
(2)

Finally calculate the tumour EQD2 delivered by your proposed modified schedule

$$\text{EQD2}_{\text{proposed}} = \sum_i d_i(1 + d_i/10)/1.2$$
(3)

where d_i is the dose (Gy)) delivered at each fraction *i*, and compare EQD2$_{\text{proposed}}$ with EQD2$_{\text{target}}$.

2. LQ calculations to check the safety of normal tissue doses

We suggest using an α/β ratio of 3 Gy for all relevant normal tissues except spinal cord, for which a 2 Gy value should be used (Binkley *et al* 2016).

2.1. Comparing a modified treatment with a protocolized dose-limit

First convert the protocol dose-limit to BED via the usual formula for a schedule delivering a uniform dose-per-fraction

$$\text{BED}_{\text{limit}} = D_{\text{limit}} [1 + (\beta/\alpha)(D_{\text{limit}}/N)]$$
(4)

where D_{limit} is the physical dose limit, and *N* the number of fractions in the protocolized schedule.

For the modified schedule being considered, calculate the relevant BED. For instance, if the limit is on maximum dose in a particular structure, calculate the BED from the maximum dose d_{Si} delivered to the structure at each fraction *i* via

$$\text{BED}_{\text{proposed}} = \sum_i d_{Si} (1 + (\beta/\alpha)d_{Si})$$
(5)

where d_{Si} will be higher for fractions after the gap than before it, if dose-per-fraction escalation is used. Then check that BED$_{\text{proposed}} \leq$ BED$_{\text{limit}}$.

2.2.   Comparing a modified treatment with a protocol limit on a volume

If the protocol limit applies to a volume, for example V_{20Gy} <35% or more generally V_{TD} <X%, where V_{TD} is the fractional volume of a structure receiving $\geq$ a threshold dose *TD* (Gy), then first convert the threshold dose to a BED via the usual LQ formula for a schedule delivering a uniform dose-per-fraction over *N* fractions

$$\mathrm{BED}_{TD} = TD\,[1 + (\beta/\alpha)(TD/N)]$$

(6)

Then calculate the total dose *TD*proposed that also has a BED of BED$_{TD}$ when delivered using your proposed escalated schedule. And check that $V_{TDproposed}$ <X%.

*TD*proposed can be calculated using the following method. Assign a weight w_1 of 1 to the first treatment fraction, delivered as planned. For all other fractions *i* of a proposed treatment, assign weights w_i, equal to the ratio of dose delivered at fraction *i* to the dose delivered by the first fraction (so weights will equal 1 before a break, and potentially be higher afterwards).

Then calculate

$$TD_{\mathrm{proposed}} = 0.5 \times \left[-\frac{\alpha}{\beta}\,A + \sqrt{\left(\left(\frac{\alpha}{\beta}\right)^2 A^2 + 4\,\frac{\alpha}{\beta}\,A \times BED_{\mathrm{TD}}\right)} \right]$$

(7)

where $\qquad A = \dfrac{\left(\sum_i w_i\right)^2}{\sum_i w_i^2}$

(8)

2.3.   Comparing a modified treatment with a protocol limit on average physical lung dose

Without using lung dose-volume-histograms there is no exact method for converting average lung doses to average BEDs or EQD2s, because different lung subvolumes are irradiated to different dose-levels. However, for treatments giving the same total prescribed dose in different schedules, the greatest variation in average lung EQD2 with schedule would occur if one lung subvolume received the prescribed dose-level, and the rest received zero dose, because BED depends quadratically on dose.

For the schedules being considered and the constraints placed on them, it has been shown that the greatest difference in EQD2 between a regularly fractionated treatment and a modified dose-per-fraction escalated schedule delivering the same total dose is <1.6 Gy. That EQD2 difference occurs for a dose of 65 Gy delivered in 20 fractions, corresponding to a prescribed EQD2 of 81.3 Gy (α/β = 3 Gy). Therefore the fractional variation in EQD2 with schedule modification is <2.0%.

For lung cancer treatments, mean lung EQD2s are generally $\leq$20 Gy. So a fractional variation of 2% in the EQD2 corresponding to the prescribed dose would lead to a $\leq$0.4 Gy change in mean lung EQD2, with little consequence for lung damage. Thus, the <u>mean physical lung dose summed over pre- and post-gap phases can be compared directly with the limit protocolized for the original schedule, provided doses-per fraction are $\leq$4 Gy, and 15- and 20-fraction schedules have not been escalated beyond 58 and 65 Gy respectively</u>.

3. Why and when to carry out LQ calculations for normal tissue doses

<u>Summary</u>

When a gap is compensated via dose-escalation achieved by adding fractions giving the same dose-per-fraction as originally planned, schedule safety can be assessed by directly comparing doses summed over pre- and post-gap treatment phases with protocol limits for the original schedule.

When dose-per-fraction escalation is used instead –

- For 15-fraction NSCLC treatments escalated to ⩽58 Gy with doses-per-fraction ⩽4 Gy, summed treatment doses can be directly compared with protocol limits (Table 2).

- For 15-fraction SCLC treatments escalated to ⩽58 Gy with doses-per-fraction ⩽4 Gy, summed treatment doses can be compared with protocol limits (Table 5) reduced by 1.3 Gy, or LQ calculations can be carried out.

- For 20-fraction NSCLC treatments delivering concurrent chemo-RT escalated to ⩽63 Gy with doses-per-fraction ⩽3.5 Gy, summed treatment doses can be compared directly with protocol limits (Table 2).

- For 20-fraction NSCLC treatments delivering RT-alone or sequential chemo-RT escalated to ⩽65 Gy with doses-per-fraction ⩽4 Gy, LQ calculations should be performed. But if summed treatment doses are directly compared with protocol limits (Table 2), the protocol limits should first be reduced by 1.6 Gy.

<u>Rationale</u>

For a particular schedule, a protocol dose-limit describes the maximum dose a tissue can tolerate when a fixed dose-per-fraction is delivered throughout the schedule. Consider a situation in which you explore escalation of a 15-fraction NSCLC schedule, initially delivered in 3.33 Gy fractions, by adding two extra fractions, each also delivering 3.33 Gy. You sum the plan over the pre- and post-gap phases, and compare a dose-metric of the plan (the maximum dose to the spinal cord, for example) with the protocol limit, and find the summed value lies exactly on the limit. It is safe to go ahead with treatment, because your modified treatment delivers exactly the same physical dose to the cord as would be just safe using the 15-fraction schedule, but you are now using 17 equal fractions and so the biological effect will be slightly lower. It is straightforward to compare dose-metrics of summed plans with protocol limits, and in general it is safe to do so if escalation has been achieved by adding fractions of the same size as the original treatment, delivering the same relative dose-distribution.

Next, consider what happens if you instead explore dose-per-fraction escalation of the 15-fraction schedule, delivering 15 fractions as originally planned, but giving larger doses-per-fraction after the gap than before it. You sum the plan and check the summed dose-metric with the protocol limit, and again find that the dose-metric lies exactly on the protocol limit. In this case, however it is <u>not necessarily safe</u> to deliver the treatment. While the total physical dose delivered by the modified 15-fraction treatment would just be tolerated when given at a

constant dose-per-fraction, in the modified treatment some fractions are larger than others. And since the biologically effective dose for a treatment is

$$\mathrm{BED} = \sum_i \quad d_i + (\beta/\alpha)\, d_i^{\ 2}$$

(9)

where d_i is the dose delivered at each fraction i, it follows that for the same total dose and number of fractions, BED will be greater for a schedule in which dose-per-fraction varies.

More generally, consider two treatments, both delivering N fractions and having the same relative dose-distribution. The first starts by delivering N_s fractions of dose d_s to the prescription point and ends with $(N-N_s)$ fractions of dose $(d_s+\Delta)$. The second delivers N factions of dose d to the prescription point, and both treatments deliver the same total dose D_{tot}. A limit $D_{limit} = f{\times}D_{tot}$ is placed on the physical dose to the most highly irradiated point in a normal tissue, and is just met by both treatments. However, although both treatments deliver the same total physical dose to the point, the irregularly fractionated treatment delivers a higher BED. For fixed values of N, f, and Δ, it can be shown that the difference in BEDs is greatest when the irregular schedule delivers the doses-per-fraction d_s and $(d_s + \Delta)$ over the first and second halves of the schedule respectively, and that this maximum difference is

$$\mathrm{BED}_{\mathrm{max-diff}} = Nf^2\Delta^2/(4\,\alpha/\beta)$$

(10)

and the corresponding difference in *EQD2*s is

$$\mathrm{EQD2}_{\mathrm{max-diff}} = Nf^2\Delta^2/(8 + 4\,\alpha/\beta)$$

(11)

For the 15-fraction NSCLC schedule, the maximum possible value of Δ is 0.67 Gy, because the unmodified schedule delivers a dose-per-fraction of at least 3.33 Gy which we suggest should not be raised to more than 4 Gy-per-fraction. The highest value of f is around 1, since relevant normal tissue dose-limits do not greatly exceed the prescribed dose. So, for an α/β ratio of 3 Gy

$$EQD2_{\mathrm{max\text{-}diff}} = 0.34 \text{ Gy}$$

This difference has little radiobiological consequence, and so for the 15-fraction NSCLC treatment, if the total dose delivered to a point by a schedule with a gap compensated by dose-per-fraction escalation meets a protocol limit for the regularly fractionated treatment, then the EQD2 delivered by the modified treatment will approximately match the EQD2 corresponding to the dose-limit of the regular treatment, and thus be just within tolerance.

The reader may have some reservations. Firstly, for spinal cord the α/β ratio is only 2 Gy, which might lead to greater EQD2 discrepancies. But for the 15-fraction NSCLC schedule, the cord dose-limit is only 42 Gy whereas the prescribed dose is $\geq$ 50 Gy, and therefore $f \approx$ 0.84 and $EQD2_{\mathrm{max\text{-}diff}}$ for the cord dose-limit works out at 0.30 Gy.

Secondly, when too few fractions remain after the break for the required degree of escalation to be achieved without increasing the dose-per-fraction by more than Δ, extra fractions may be added, and it might be thought that this could increase the EQD2. Consider initially a schedule (I) with a break that occurs just early enough for the gap to be

compensated by dose-per-fraction escalation of the remaining fractions. Then consider a schedule (II) with a later break that requires fractions to be added to achieve the same level of escalation. The EQD2 of the schedule (II) will be *lower* than that of schedule (I), since schedule (II) delivers the same dose in more fractions. And therefore, the EQD2 of schedule (II) will exceed the EQD2 of a treatment delivering the same dose in the original number of equal fractions by *less* than does the EQD2 of schedule (I), and thus by *less* than EQD2$_{max-diff}$.

In summary, then, for the 15-fraction NSCLC schedule, the safety of dose-per-fraction escalated treatments can be assessed by comparing doses summed across pre- and post-gap phases with protocol limits, provided the dose-per-fraction is not increased beyond 4 Gy nor the prescribed dose beyond 58 Gy.

Repeating this analysis for the 20-fraction concurrent chemo-RT NSCLC schedule, for which the maximum increase in dose-per-fraction is 0.75 Gy (from 2.75 to 3.5 Gy), an EQD2$_{max-diff}$ value of 0.56 Gy is obtained for an α/β ratio of 3 Gy and a dose-limit at the level of the prescribed dose; and an EQD2$_{max-diff}$ value of 0.41 Gy is obtained for an α/β ratio of 2 Gy and a spinal cord dose-limit of 42 Gy compared to a prescribed dose of 55 Gy. Again, these differences have little radiobiological consequence, and so for this treatment too, summed dose-metrics can be compared directly with protocol dose-limits.

Considering the 20-fraction NSCLC schedule delivering RT-alone or sequential chemo-RT, for which the maximum possible increase in dose-per-fraction is 1.25 Gy (from 2.75 to 4 Gy), an EQD2$_{max-diff}$ value of 1.56 Gy is obtained for an α/β ratio of 3 Gy and a dose-limit at the level of the prescribed dose; and an EQD2$_{max-diff}$ value of 1.43 Gy is obtained for an α/β ratio of 2 Gy and a spinal cord dose-limit of 47 Gy compared to a prescribed dose of 55 Gy. Radiobiologically, these differences are borderline consequential, and so we suggest carrying out LQ calculations for this 20-fraction NSCLC treatment when dose-per-fraction escalation is used to compensate gaps. If instead summed dose-levels are directly compared with protocol dose-limits to assess safety, the protocol limits should be reduced by 1.6 Gy.

Finally turning to the 15-fraction SCLC treatment, which permits a 1.33 Gy maximum increase in dose-per-fraction (from 2.67 to 4 Gy), an EQD2$_{max-diff}$ value of 1.33 Gy is obtained for an α/β ratio of 3 Gy and a dose-limit at the level of the prescribed dose; and an EQD2$_{max-diff}$ value of 1.34 Gy is obtained for an α/β ratio of 2 Gy and a spinal cord dose-limit of 36 Gy compared to a prescribed dose of >40 Gy. These differences approach a radiobiologically consequential level, and therefore for 15-fraction SCLC treatments in which dose-per-fraction escalation has been used to compensate gaps, we suggest either carrying out LQ calculations, or reducing protocol limits by 1.3 Gy before directly comparing them with dose-levels summed over pre- and post-gap phases.