Guidance on the Management of Treatment Gaps and Interruptions in Radical Fractionated Radiotherapy Arising from the COVID 19 Pandemic

This document relates to patients who do not have COVID-19 or are not suspected of having COVID-19.

Current events surrounding the COVID-19 pandemic are challenging and all public health bodies are placing the safety of patients, staff and communities first in all decisions.

This is an evolving situation. This advice is based on current information, it is additional to the advice of the NPHET, the HSE and the DoH, and will be updated as necessary.

The NCCP acknowledges that each hospital is working under individual constraints, including staff and infrastructure, and as a result will implement this advice based on their own unique circumstances.

The purpose of this advice is to maximise the safety of patients and make the best use of HSE resources, while protecting staff from infection. It will also enable services to match the capacity for cancer care to patient needs if services become limited due to the COVID-19 pandemic.

Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment.

NPHET, HSE and DoH advice

Hospitals will operate under the overarching advice of the National Public Health Emergency Team (NPHET), the HSE and the DoH. Information is available at:

- HSE HPSC - https://www.hpsc.ie/a-/respiratory/coronavirus/novelcoronavirus/guidance/
- HSE Coronavirus (COVID-19) - https://www2.hse.ie/conditions/coronavirus/coronavirus.html
- DoH Coronavirus (COVID-19) - https://www.gov.ie/en/campaigns/c36c85-covid-19-coronavirus/
- Ireland's National Action Plan in response to COVID-19 (Coronavirus) - https://www.gov.ie/en/campaigns/c36c85-covid-19-coronavirus/

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1.0 Purpose / Aim

The purpose of this document is to ensure that radical fractionated radiotherapy treatment interruptions arising from the COVID 19 pandemic are managed appropriately, consistently and in line with international best practice. The aim is to devise a method for the timely calculation and implementation of compensation strategies that ensure therapeutic ratios are maximised and that our patients continue to experience optimal clinical outcomes.

2.0 Scope

This document applies to all radical radiotherapy undertaken in SLRON. It does not apply to stereotactic radiotherapy or brachytherapy.

This document pertains to the work of all radiation oncologists, physicists, planners, and radiation therapists working in St Luke's Radiation Oncology Network.

It is the responsibility of all line managers to bring this document to the attention of their staff and for all staff to read, understand and adhere to it's content.

3.0 Legislation/other related policies and References

- RAD ONC 017 Guideline for the Management of Radiotherapy Treatment Gaps
- PHYS SLRON TP 238 Procedure for Radiobiological Calculations in Clinical Practice
- COVID F 19 COVID-19 Radiotherpay Treatment Gap Compensation Form
- RCR (UK) 2019 The timely delivery of radical radiotherapy: guidelines for the management of unscheduled treatment interruptions 4th Ed

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4.0 Glossary of Terms and Definitions

BC	SLRON at Beaumont Hospital
CT	Computed Tomography
NEMT	Network Executive Management Team
QART	Quality Assurance in Radiation Therapy
RA	Risk Assessment (for FMEA)
RT	Radiation Therapy / Radiotherapy
RTSM	Radiation Therapy Services Manager
SJC	SLRON at St James’ Hospital
SLH	SLRON at St. Luke’s Hospital
SLRON	St Luke’s Radiation Oncology Network
TPS	Treatment Planning System

5.0 Introduction

The importance of overall treatment time in radiotherapy has been long recognised [1]. Numerous historic studies have demonstrated an inverse relationship between overall treatment time and clinical outcome [2,3]. This is attributed to the phenomenon of repopulation where stem cells associated with tumour growth begin to repopulate generally 2-3 weeks after radiotherapy has commenced. The result of this is that the radiation dose per fraction is less effective at controlling tumour growth in the final weeks of treatment than it was in the initial period before the onset of repopulation.

In this context, interruptions or treatment gaps in radiotherapy can have a significant impact on clinical outcome by prolonging the overall treatment time. It is generally accepted however, that radiotherapy should not be interrupted and where interruptions are unavoidable, compensatory treatments are required.

The Royal College of Radiologists UK published guidelines for the management of treatment interruptions in 1996 with revisions in 2002, 2008 and 2019 [4]. This document has been used extensively since its first publication across the international community and indeed forms the basis of the SLRON policy RAD ONC 017 Guideline for the Management of Radiotherapy Treatment Gaps.

While the RCR document is useful in promoting a standardised approach it was devised for use in the setting of short treatment breaks in the order of 1-5 days. In the last several days the RCR have published on their website a table of suggested radiobiological parameters to be used for treatment interruptions during the course of the COVID 19 pandemic (this table is reproduced here in section Table 1 Section 7.0).

While this forms the basis for increased standardisation there is little clinical experience either locally or in the literature of devising compensation strategies for such prolonged treatment gaps. This is currently a matter of some debate in the radiotherapy community. The approach undertaken in this document will be to use the methodology of RCR (2019) but to review the results critically using clinical judgement and compare against current international approaches, as they exist. In particular, we reference the recent paper by Gay et al (2019) [5] where compensation strategies developed for patients who had prolonged treatment gaps as a result of Hurricane Maria in Puerto Rico in 2017 are outlined.

This document is intended to cover the period of the COVID 19 pandemic and create a structure for a standardised approach to compensation for prolonged interruptions. It consists of a multidisciplinary departmental workflow, a method for devising and calculating compensation strategies, an evaluation of radiobiological parameters per tumour site, tumour site-specific examples and reproduction of a reference table from the work of Gay et al [4] mentioned above.

6.0 Multidisciplinary Departmental Work Flow

In figure 1 below the planning worklow for compensation is presented.

The steps are described below (please note that workflow outlined here is designed on the ARIA-ECLIPSE configuration however these concepts are easily translatable to Monaco/Oncentra framework) :

- Once a patient is on hold for COVID 19 reasons the radiation therapists on the treatment unit will insert the BC/SJC/SLH COVID 19 Treatment Gap Carepath template (all but treatment unit is pre resourced).
- Physicist responsible will check the COVID tracker on a daily basis
- If a patient return date has been established and recorded the physicist will upload COVID F 034, conduct the compensation calculation and have it checked by an independent physicist.
- The independent physics check should be obtained before the compensation strategies have been presented to the RO and should be based on all available information.
- Physics will complete section A of COVID F 34 and complete their COVID Treatment Gap task.
- RO alerted by taskpad and completes section B acknowledging and approving the compensation strategy. Completes the COVID Treatment Gap task.
- Planning alerted and according to selected compensation strategy will (1) take no action (2) replan or (3) prepare a plan revision.
- Planning completes section C adding patient to planning meeting for peer review.
- ROs will complete section E when compensation has been peer reviewed.
- Treatment unit RTs are alerted by taskpad and will amend bookings and complete section D of COVID F 34.
- Patients return date should never be delayed waiting on the compensation strategy. If this is not available the patient should recommence treatment using the same dose per fraction as the reference phase.
- For sequential phase treatments it is generally accepted that compensation for each phase should be considered separately.

- Compensation strategies will consist of one of four techniques as follows: Simple acceleration, iso-fractionated dose escalation, dose escalation by increased dose per fraction or compensation by another technique.
- The workflow for each of these options is outlined below:
  - Simple acceleration
    - This involves delivering the remaining fractions in the original overall time T by bi-dailies
    - If compensation can be achieved by simple acceleration, no plan revision is required.
    - Please note that only 6 fractions per week are permitted. This includes weeks with bank holidays.
  - Iso-fractionated dose escalation
    - If extra fractions are required a plan revision will be produced by planning and a plan sum for the total dose produced.
    - If fractions size allows (i.e. d<2.2 Gy) these fractions may also be delivered in an accelerated fashion.
    - RO will review the plan sum with particular reference to dose to OARs.
  - Escalation of dose by increased dose per fraction (Hypo-fractionation)
    - If dose per fraction is increased a replan for the compensation strategy will be produced by planning
    - Physics will perform a radiobiological summation of appropriate OAR point doses and annotate this in the journal. It is expected that acceleration will not be allowed with this technique (i.e. d> 2.2 Gy)
  - Other techniques
    - For cervix and prostate patients this will involve brachytherapy. This is beyond the scope of this document and can be dealt with by the brachytherapy multidisciplinary team should the need arise.
    - For breast patients this will involve the planning of a boost plan, which was not indicated in the original treatment or the addition of fractions to an already planned boost.
- In either case plan revision or replan will be produced by physics/planning and a plan sum created.
- RO to review and approve and annotate approval in the journal.
- Physics to approve plan and/or perform plan check as appropriate

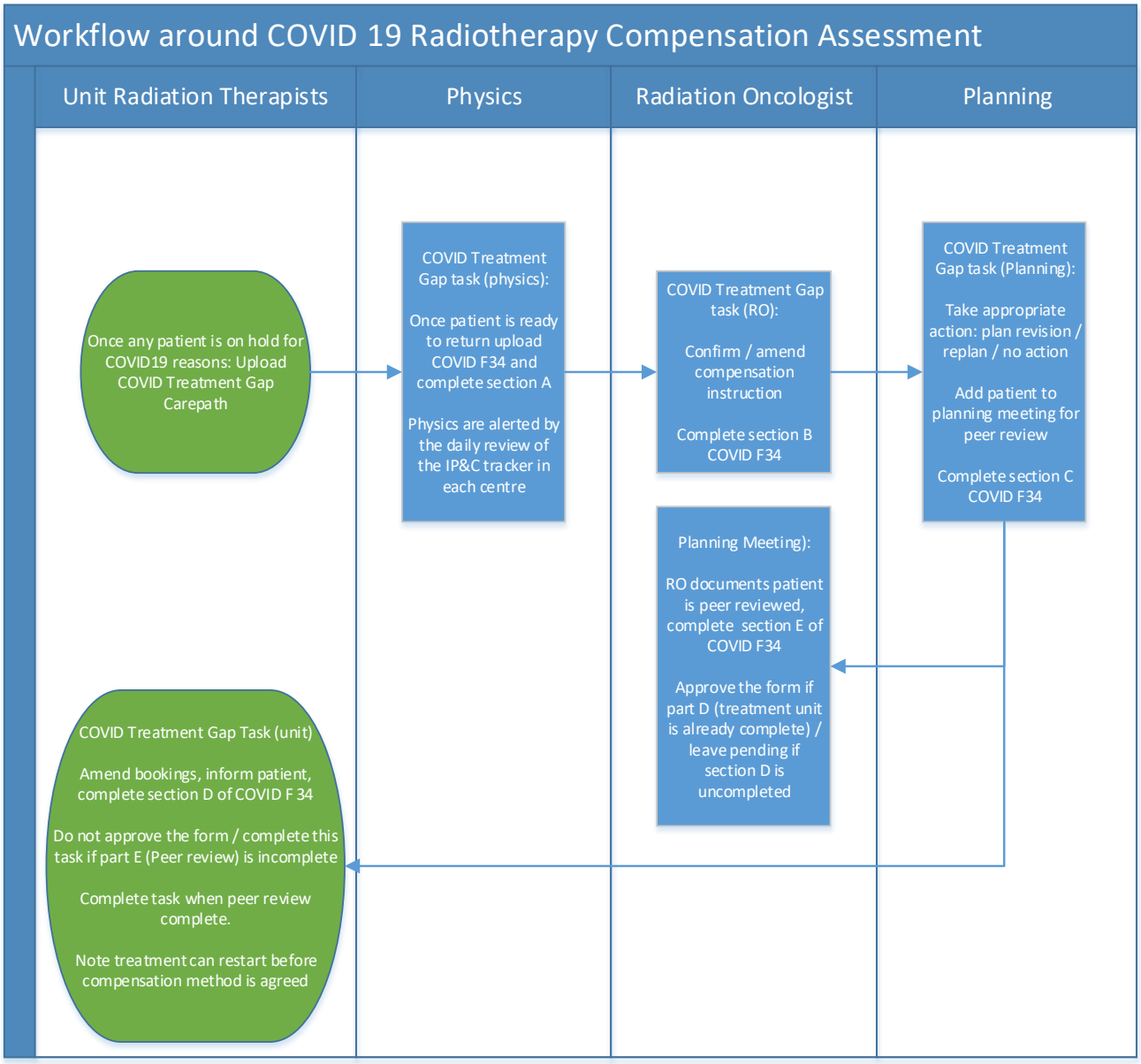

Figure 1: Workflow for COVID 19 Gap Compensation

7.0 Radiobiological Parameters

In the light of the recent pandemic the RCR [10] have published additional guidance on the management of unscheduled radiotherapy interruptions. This consists of a table of radiobiological parameters for use in compensation calculations. This table is reproduced overleaf in table 1.

It is recommended for consistency and uniformity with international practice that these values be used for all compensation calculations in SLRON.

Organ at risk calculations should use the values referenced in PHYS SLRON TP 238 for α/β ratios i.e. CNS (2) all other OAR (3).

Tumour and Clinical Setting	SLRON Tumour Classification	α/β Ratio (Gy)	K-value (Gy per day)	TR
Squamous cell carcinomas (NSCLC) including adenocarcinomas in lung		10	0.9	28
Transitional Cell carcinomas		10	0.36	35
Adenocarcinoma Breast (Post Op)		4	0.6	21
Adenocarcinoma Breast (Intact cancer)		4	0.3 or 0.6(if T>42 days)	21 42
Adenocarcinoma Prostate (Well differentiated)		2	0.3	42
Adenocarcinoma Prostate (Moderately and poorly differentiated)		4	0.5	42
Other adenocarcinomas (if poorly differentiated use prostate row)		4	0.3	41
Others in category 1 (rapidly growing tumours or with anaplastic features).		10	0.9	28

Table 1. Recommended Radiobiological Parameters per Tumour Site

8.0 Calculating Compensation Strategies

8.1 Calculating BEDs

8.1.1 Tumour BED

The calculation of compensation strategies begins with Dale's [6] formalism of the linear quadratic cell-killing model to incorporate repopulation. In this formalism the biological effective dose (BED) of a treatment course is given the conventional linear quadratic equation mitigated by a repopulation term $K(T-T_R)$ as follows:

$$BED = nd(1+d/(\alpha/\beta)) - K(T-T_R) \qquad (1)$$

n= number of fractions	K= Repopulation Factor Gy Day-1
d=dose per fraction	T = Total Treatment Time (days)
$\alpha/\beta = 10$	T_R = Repopulation Time

The repopulation factor K is considered to be the extent to which the biological effect of the daily dose d is reduced by repopulation. K is a tumour site specific factor and there is currently much debate concerning the appropriate value of this term in any specific case. T is the total treatment time of course of radiotherapy (i.e. the total number of days including weekends and bank holidays from the first delivered fraction to the last). T_R is the time in days from the first fraction of radiotherapy until the onset of repopulation. This again is tumour site specific and again there is much debate as to the appropriate value to use. Values of K and T_R to be used in SLRON are outlined in table 1 section 7.0. Please note that the repopulation term - $K(T- T_R)$ cannot be positive so for $T_R > T$, $K = 0$.

8.1.2 OAR BED

Organ at risk BED calculations should use the values referenced in PHYS SLRON TP 238 for α/β ratios i.e. CNS (2) all other OAR (3). Although repopulation occurs in OARs a matter of hours after initial irradiation not enough is known of this phenomenon to apply it in these calculations.

It should be noted that although calculation of OAR BEDs provide indicative values in order to compare compensation strategies a full evaluation of OAR DVCs against institutional tolerances is required after the replan or plan revision is completed. This may involve radiobiological summation if differing dose per fraction (d) are used.

8.2 Definitions

Reference Course: the intended prescription of radiotherapy approved at the start of treatment by the RO e.g. 60 Gy in 30 fractions given daily (5 fractions a week) to a total treatment time T of 40 days. The total treatment time T is the time in days from the first to the last delivered fraction including all weekends and bank holidays. The reference tumour BED will be calculated for the reference course, and will be used as benchmark for evaluation of the optimal compensation strategy

Original Phase: Delivered radiotherapy before onset of the treatment interruption e.g. 10 Gy in 5 d=fractions delivered over 7 days.

Interrupted Phase: number of days of no treatment

Compensation Phase: compensation course of radiotherapy as calculated and agreed between ROs and physics e.g. 50 Gy in 25 fractions over 33 days.

8.3 Methods of Compensation

The aim of any compensation strategy is to deliver an equivalent or near BED to the tumour whilst maintaining the dose to the normal tissue below acceptable tolerances. This can be achieved in the compensation phase by one of four ways as follows:

1. Simple acceleration
2. Iso-fractionated dose escalation (with or without Acceleration)
3. Hypofractionated dose escalation (without acceleration)
4. Use of alternate treatment techniques

Refer also to RAD ONC 017 Guideline for the Managerment of Radiotherapy Treatment Gaps

8.3.1 Simple Acceleration

Simple Accelerated schedule involves delivering the compensation phase over an accelerated time by delivering 6 fractions per week (including weeks with bank holidays), either treating bi-daily (6 hours apart). With this approach the original total dose (D) and dose per fraction (d) are maintained. Acceleration is not recommended for dose per fraction of more than 2.2 Gy as per RCR 2019 [4].]. It is noted that simple acceleration may result in local scheduling difficulties. For this reason a final decision on compensation must be taken on a case by case basis with reference to logistical and organisational capabilities also. For head and neck patients refer to COVID WI 19 Radiotherapy for Head and Neck Patients during the COVID 19 Emergency.

8.3.2 Iso-fractionated dose escalation (with or without Acceleration)

In order to match the reference tumour BED (see above for definition) it may be necessary to escalate the total dose.

With the iso-fractionated dose escalation approach the original dose per fraction (d) is maintained and the total prescribed dose D is escalated. This will result in the dose to the normal tissue being increased. A simple plan revision for the new total dose (D) will be provided. For each organ at risk the relevant dose parameters (maximum, mean, and dose volume (e.g. V_{30}) can be directly extracted and analysed from the DVHs and be compared to institutional DVCs. However in case the DVCs are exceeded, radiobiological conversion remains useful to inform on potential toxicity (Example: For 55 Gy/20 NSCLC radiation schedule the spine DVC is 48 Gy in 20 (BED 105.6 Gy_2), in case of dose escalation by 2 fractions (TD dose 60.5 Gy /22), the equivalent BED for the spine DVC is in arithmetic value 49 Gy /22).

An advantage to this technique is that a replan is not required, DVCs to OARs can be more easily interpreted and acceleration can be considered (if applicable see 8.1.3.1).

8.3.3 Hypofractionated dose escalation (without acceleration)

With the hypo-fractionated dose escalation approach both the dose per fraction (d) and the total prescribed dose D are escalated for the compensation phase, in order to match the reference tumour BED.

The consequence however will be that the dose to the OARs, both arithmetically and biologically, will also increase. In using this strategy use the following steps

1. Calculate d required for the compensation phase such that the sum of the BEDs from the original, interruption and compensation phases are equal to the BED from the reference course. In first instance, a dose per fraction (d) of 2.5 Gy will be evaluated but higher values of d may be considered.
2. Determine the maximum permissible OAR dose points for the hypo-fractionated plan and provide these to the planners.
3. Planning to create a new hypo-fractionated plan for the compensation phase ensuring if at all possible that the OAR values are maintained below those determined by physics above.
4. Provision of a cumulative dose plan, combining original phase and compensation phase plans
5. Determine the BEDs for relevant dose points for OARs from both the original and compensation phase.
6. Sum the BEDs and compare to institutional tolerances (DVC and Re-irradiation table).

An advantage of this technique is that in circumstances with large gaps equivalent tumour BEDs may be obtained when compared to the reference. OARs may however exceed or be at the cusp of tolerance and should be carefully considered by the RO. Please be aware that in this case, points on the OAR DVH other than the maximum points cannot be evaluated.

Hypofractionated dose escalation may be not applicable

- In tumour site and/or clinical scenario where the use of hypofractionation is not validated (e.g. paediatric, postoperative NSCLC)
- In the situation of combined modality where the use of hypofractionation is not validated (e.g combined concomitant SWOG chemotherapy and radiotherapy in NSCLC)

In relation to structures generated by planning for IGRT purposes such as the 50 Gy isodose line. It is recommended that the physicist review such structures for compensated patients and adapt or regenerate radiobiologically determined structures as appropriate. This will likely involve radiobiological calculations when replans are produced with changed dose per fraction.

8.3.4 Use of alternate techniques

For some tumour sites such as breast, prostate or cervix, compensation can be achieved by using boost plans or brachytherapy.

- ***Breast:*** In cases where adding extra fractions may result in significant increases in the OAR dose consideration may be given to delivering the extra fractions to the boost phase or indeed adding a boost component where one was not originally prescribed in the reference course. This might be particularly relevant for left sided breasts where cardiac dose is a consideration. This was the approach taken by Gay et al [5] see reproduced table (appendix 2).
- ***Cervix:*** The addition of extra fractions to the brachytherapy component or adjusting the brachytherapy dose per fraction can be utilised. This can compensate for loss of BED to the tumour due to interruption whilst also resulting in a lower BED to OARs than would have been obtained had extra or hypofractionated fractions been added to the EBRT compensation phase.
- ***Prostate:*** Low dose rate permanent seed implantation salvage therapy can be considered for patients with low and intermediate risk prostate cancer who have had severely prolonged interruptions.

9.0 Site Specific Examples

9.1 Lung

- Example 1
  - *Reference Phase*
    - Patient originally prescribed 60 Gy in 30 fractions with an overall treatment time T of 40 days. Reference tumour BED Gy_{10} = 61.2 Gy_{10} and OAR BED Gy_3 = 100 Gy_3 & BED Gy_2 = 120 Gy_2.
    - Alpha/beta for tumour used is 10 and 3 for normal tissue and 2 for CNS tissue. The used tumour repopulation parameters are T_R = 28 K =0.9.
  - *Original Phase*
    - 10 Gy in 5 fractions delivered followed by a 18 day interruption.
    - Tumour BED Gy_{10} = 12Gy_{10} OAR BED Gy_3 = 16.7Gy_3 OAR BED Gy_2 = 20 Gy_2
  - *Compensation Phase*
    - Compensation required BED Gy_{10} = 61.2 -12 = 49.2 Gy_{10}
    - OAR "credit" BED Gy_3 =100-16.7 = 83.3 Gy_3
      BED Gy_2 = 120 – 20 = 100 Gy_2

<u>Option 1 Iso-Fractionation with accelerated scheduling maintaining D</u>.

	d	n	T	BED Gy10	BED Gy3	BED Gy2
Reference Course	2	30	40	61.2	100	120
Original Phase	2	5	5	12	16.7	20
Gap	18 days			0	0	0
Compensation Phase	2	25	30	37.5	83.3	100
TOTAL	2	30	53	49.5	100	120
				BED - 20%	BED0%	BED 0%

In option 1 above as d<2.2 Gy the compensation phase was delivered at an accelerated rate of 6 fractions per week.

Option 2 Iso-Fractionation with accelerated scheduling increasing D.

	d	n	T	BED Gy10	BED Gy3	BED Gy2
Reference Course	2	30	40	61.2	100	120
Original Phase	2	5	5	12	16.7	20
Gap	18 days			0	0	0
Compensation Phase	2	30	36	44.1	100	120
TOTAL	2	35	59	56.1	116.7	140
				BED -8.3%	BED+16.7 %	BED +16.6%

In option 2 above as d<2.2 Gy the compensation phase was delivered at an accelerated rate of 6 fractions per week.

Option 3 Hypofractionation for the compensation phase

	d	n	T	BED Gy10	BED Gy3	BED Gy2
Reference Course	2	30	40	61.2	100	120
Original Phase	2	5	5	12	16.7	20
Gap	18 days			0	0	0
Compensation Phase	2.5	24	34	48.9	110	135
TOTAL		29	57	60.9	127	155
				BED -0.4%	BED + 27%	BED + 29.2 %

In option 3 fractionation cannot be accelerated as d>2.2 Gy

In this case plans were prepared for both option 2 and 3. Option 3 was considered the preferable option as the tumour dose was matched and the relevant point doses to the significant OARs i.e. spinal cord, oesophagus, heart, airway and lungs were converted to BEDs, summed and compared to institutional tolerances. Combined doses to the Oesophagus and lungs were deemed unacceptable by the RO. Option 2 was chosen despite the loss in tumour dose as doses to the OARs were in tolerance.

9.2 Prostate

- Example 2: Prostate bed patient
    - *Reference Phase*
        - Prescribed treatment is 64Gy in 32#s with an overall treatment time T of 49 days. Reference BED Gy_2 = 125.9 (Tumour) and BED Gy_3 = 106.7 (NT)
        - Alpha/beta for tumour used is 2. T_R = 42 K =0.3 (see table 1 section 7.0)
    - *Original Phase*
        - Patient had 26 fractions delivered over 41 days.
        - Original Phase BED Gy_2 = 104 (Tumour) BED Gy_3= 86.7 (NT)
    - *Interrupted Phase*
        - 15 day interruption BED Gy_2 = -4.2 (Tumour) BED Gy_3= 0.0 (NT)
    - *Compensation Phase*
        - Compensation required BED Gy_2 = 125.9 – (104-4.2)= 26.1 Gy_2 (Tumour)
        - BED Gy_3 =106.7-86.7 = 20 Gy_3 (NT)

Option 1 Iso-Fractionation with accelerated scheduling maintaining D.

	d	n	T	BED Gy2 Tumour	BED Gy3
Reference Course	2	32	49	125.9	106.7
Original Phase	2	26	41	104	86.7
Gap	15 days			-4.2	0
Compensation Phase	2	6	5	22.5	20
TOTAL	2	30	53	122.3	106.7
				BED -3%	BED 0%

With option 1 tumour dose is approximately 3% low and NT toxicities are matched. RO considered this clinically acceptable.

9.3 Head & Neck

- Example 3: A Head and Neck patient.
    - Alpha/beta for tumour used is 10. T_R = 28 K =0.9 (see table 1 section 7.0)
    - *Reference Phase* 70Gy in 35#s over 49 days. Reference BED Gy_{10} = 65.1 and normal tissue BED Gy_3 = 116.67 and BED Gy_2 = 140
    - *Original Phase*
        - Patient had 16 fractions delivered over 23 days
        - Original Phase BED Gy_{10} = 38.4 BED (Tumour) BED Gy_3= 53.3 BED Gy_2 =64. (Normal Tissue)
    - *Interrupted Phase*
        - 8 day interruption BED Gy_2 = -2.7 (Tumour) BED Gy_3, Gy_2= 0.0 (NT)
    - *Compensation Phase*
        - Compensation required BED Gy_{10} = 65.1-(38.4-2.7) = 29.4 Gy_{10}
          BED Gy_3 =116.7-53.2 = 20 Gy_3
          BED Gy_2 = 140-64 = 76Gy_2

Option 1 Simple Acceleration Same D and d

	d	n	T	BED Gy10 Tumour	BED Gy3 Normal Tissue	BED Gy2
Reference Course	2	35	49	65.1	116.7	140
Original Phase	2	16	23	38.4	53.3	64
Gap	8 days			-2.7	0	0
Compensation Phase	2	19	21	29.1	63.3	76
TOTAL	2	35	52	64.8	116.7	140
				TCP 0%	NTCP 0%	NTCP 0%

In this case of simple acceleration the addition of 4 bi-daily fractions in the compensation phase compensates for the gap. BEDGy_{10} is matched and as D remains constant. OAR values will be matched to the reference phase

9.4 Brain Compensation Calculation

- Example 4 Brain patient with two issues:
    - Contour change requiring a replan

- Gap in treatment due to COVID diagnosis

- Timeline of events:
  - 1st fraction on Thursday 12th March
  - Missed fraction for Tues 17th March
  - Thus received 6# on plan 1 from 12th – 20th March
  - Received a new CT Sim but also on hold due to COVID, replan preparation continued
  - Restarted Tues 31st on replan
  - New hypofractionated plan in 15# to complete with only one extra day to start Fri 3rd April

Intended Fractions							Fractions						
MON	TUES	WED	THURS	FRI	SAT	SUN	MON	TUES	WED	THURS	FRI	SAT	SUN
			1	2						1	2		
3	4	5	6	7			3		4	5	6		
8	9	10	11	12									
13	14	15	16	17				1	2	3	1		
18	19	20	21	22			2	3	4	5	6		
23	24	25	26	27			7	8	9	10	11		
28	29	30					12	13	14	15			

Target:

$$BED = nd\left(1 + \frac{d}{\alpha/\beta}\right) - K(T - T_R)$$

- In CNS repopulation is 0.7 BED Gy10 per day beyond kick-off
- Kick-off time is 25 days
- Initial fractionation schedule included an elapsed timeframe of 42 days
- Thus BED lost to repopulation = 0.7*(42-25) = 11.9 Gy10
- Proposed schedule by RO will extend treatment time by a further day, thus repopulation = 0.7*(43-25) = 12.6 Gy10
- RO selected a compensation schedule of 39/30 in 15# based on clinically used schedules and acceptable total BEDs

	Planned BED	**Summed BED**
PTV High	60.1	58.14
PTV Int	51.82	42.516

Original Plan

	D	n (planned)	d	n (actual)	D(actual)	Repop	BED	Bed incl Repop
PTV High	60	30	2	30	60	-11.9	72	60.1
PTV Int	54	30	1.8	30	54	-11.9	63.72	51.82

Plan 1 (6 fractions)

	D	n (planned)	d	n (actual)	D(actual)	Repop	BED	Bed incl Repop
PTV High	60	30	2	6	12	0	14.4	14.4
PTV Int	54	30	1.8	6	10.8	0	12.744	12.744

Plan 2 (3 fractions)

	D	n (planned)	d	n (actual)	D(actual)	Repop	BED	Bed incl Repop
PTV High	48	24	2	3	6	0	7.2	7.2
PTV Int	43.2	24	1.8	3	5.4	0	6.372	6.372

Plan 3 (15 fractions)

	D	n (planned)	d	n (actual)	D(actual)	Repop	BED	Bed incl Repop
PTV High	39	15	2.6	15	39	-12.6	49.14	36.54
PTV Int	30	15	2	15	30	-12.6	36	23.4

OARs:

$$EQD_2 = D\left(\frac{d+\alpha/\beta}{2+\alpha/\beta}\right) = nd\left(\frac{d+\alpha/\beta}{2+\alpha/\beta}\right)$$

- Knowns are:
  - Already received dose
  - Tolerance of organ (serial only)
  - Number of fractions we wish to treat in
  - α/β taken as 2 to be conservative
- Unknown is:
  - Dose per fraction each plan can receive in the replan, solve the quadratic for 'd'

Brainstem

Plan 1 (6 fractions)						
	D	**n (planned)**	**d**	**n (actual)**	**D(actual)**	**EQD2 received (a/b =2)**
B/S	58.5	30	1.950	6	11.70	11.554

Plan 2 (3 fractions)						
	D	**n (planned)**	**d**	**n (actual)**	**D(actual)**	**EQD2 received (a/b =2)**
B/S	46.8	24	1.950	3	5.85	5.777

	Limits in EQD2	**Plan 1**	**Plan 2**	**Remaining**
B/S	60	11.554	5.777	42.669

given n is fixed at 15 solve the EQD2 equation to find d				
	d	**n**	**D**	**EQD2**
B/S	2.518	15	37.77	42.661

9.5 Breast

- Example 5: Breast patient 1
  - Alpha/beta for tumour used is 4. T_R = 21 K =0.6 (see table 1 section 7.0)
  - *Reference Phase* Right breast patient 40Gy in 15 fractions plus a boost of 11.25Gy in 5 fractions.
    - Tangential Treatment 40 Gy in 15 fractions over 21 days. Reference BED Gy4 = 66.8 and normal tissue BED Gy_3 = 75.7.
    - Boost Phase 11.25 Gy in 5 fractions over 5 days (repopulation has to be taken into account here). Reference BED Gy_4 = 14.6 and normal tissue BED Gy_3 = 19.7.
    - Reference dose to lumpectomy site = 66.8+14.6 = 81.4 Gy_4
  - *Original Phase*
    - Patient had 13 fractions delivered over 17 days – Tangential Treatment
    - Original Phase BED Gy_4 = 57.8 (Tumour) BED Gy_3= 65.6 (Normal Tissue).
  - *Interrupted Phase*
    - 21 day interruption BED Gy_4 = -10.2 (Tumour) BED Gy_3 = 0.0 (NT)
  - *Compensation Phase*
    - Compensation required BED Gy_4 = 66.8-(57.8-10.2) = 19.2 Gy_4

Option1 Same d increase D

	d	n	T	BED Gy4 Tumour	BED Gy3
Reference Course	2.67	15	21	66.7	75.7
Original Phase	2.67	13	17	57.9	65.6
Gap	21 days			-10.2	0
Compensation Phase	2.67	5	5	19.3	25.23
TOTAL	2.67	18	43	67	90.8
				BED -0%	BED +20%

In this option a total of 48.06 Gy in 18 fractions will be delivered. BED to the tumour is matched and a plan revision for the new total dose indicated doses to the lung and skin below institutional tolerances. The boost phase was given as prescribed (11.25 Gy in 5 fractions) directly after the compensation phase as the effects of repopulation are already accounted for in boost treatments.

- Example 6: Breast Patient 2
    - Alpha/beta for tumour used is 4. T_R = 21 K =0.6 (see table 1 section 7.0)
    - *Reference Phase* Right breast patient 40 Gy in 15 fractions delivered to Chest Wall and supraclav over 21 days.
        - Reference BED Gy_4 = 66.8 and normal tissue BED Gy_3 = 75.7.
    - *Original Phase*
        - Patient had 7 fractions delivered over 9 days – Tangential Treatment
        - Original Phase BED Gy_4 = 31.2 (Tumour) BED Gy_3= 35.32 (Normal Tissue).
    - *Interrupted Phase*
        - 9 days of treatment + 8 day gap = 17 (still before the onset of repopulation. BED Gy_4 = 0 (Tumour) BED Gy_3 = 0.0 (NT)
    - *Compensation Phase*
        - Compensation required BED Gy_4 = 66.8-31.2 = 35.6 Gy_4

	d	n	T	BED Gy4 Tumour	BED Gy3
Reference Course	2.67	15	21	66.7	75.7
Original Phase	2.67	7	9	31.2	35.3
Gap	8 Day Gap			0	0
Compensation Phase	2.67	9	11	35.9	45.42
TOTAL	2.67	16	28	67	80.7
				BED -0%	BED +6

In this example compensation for the 8 day gap consisted of 1 extra fraction added to thje end of treatment. Tumour BEDs were matched and although NT BEDs were 6% higher than the reference phase review of the plan revision indicated acceptable doses to the OARs (i.e. skin, lung, chest wall).

10.0 Appendices

Appendix 1. Institutional Tolerance Tables

	alpha/Beta	Optimal (BED)	Mandatory (BED)
Spine	2	64	120
Brachial Plexus	3	57	112
Oesophagus	3	95.8	122.4
Airway/Trachea	3	74.7	145.8
Trachea and Large Bronchus	3	34.7	146.7
Bronchus Small Airway	3	50.4	82.4
Heart	3	75.6	210
GreatVessels	3	240.3	270
Rib/Chest Wall	3	102.4	189.1
Skin	3	88	144
Stomach	3	77	116.7
Normal Lungs -GTV	3		
Liver	3		

	alpha/Beta	Optimal (BED)	Mandatory (BED)
Spinal Cord	2	64	120
Cauda Equine	2	120	150
Small Bowel	3	92	106
Sigmoid	3	92	106
Rectum	3	124	133
Bladder	3	124	133
R Fem Head	3	72	92
L Fem head	3	72	92
Skin	3	88	144

Appendix 2: Reproduction fom Gay et al [5]

Table 3 Compensate: Step 4 of PCOC, assuming a 2-3 week delay in radiation therapy

Cancer	Clinical scenario	Impact of gap	Recommendations
NSCLC	Locally advanced, postoperative	Low	Restart therapy when possible. Given that these are usually patients with concern for microscopic disease who have already received (or are receiving) chemotherapy, the impact of a treatment break and concerns about tumor repopulation are lower than those for patients with gross disease.
	Locally advanced, definitive	High	Restart these patients sooner than the postoperative patients. **Concurrent chemotherapy group:** Recommend restarting with standard fractionation. If the patient has a prolonged delay, consider adding a cycle of chemotherapy at a systemic dose during the treatment break. **RT alone group:** RT-alone group (or sequential chemoRT group). Consider modest hypofractionation of no more than 2.53 Gy per fraction to a total dose of 63.25 Gy without chemotherapy and **no** highly conformal treatment techniques.[27] For highly conformal image guided/intensity modulated RT techniques, consider 60 Gy in 15 fractions without chemotherapy.[28] Consider these schedules especially for larger or more aggressive tumors.
SCLC	Limited stage	Very high	Restart thoracic as soon as possible (even midcycle) and preferentially switch to twice a day per Turrisi.[29] Consider following curative chemoradiation regimens of 40 Gy in 15 fractions,[30] 40 Gy in 16 fractions,[31] or 42 Gy in 15 fractions,[32] or 39.9 Gy in 15 fractions.[33] The potential advantage of these schedules is that the dose constraints are usually easily met (cord <36 Gy; V18<37%). A patient who had a few fractions followed by a long break often can safely receive this schedule upon restart with an acceptable composite plan.
	Extensive stage	Very high	If the delay caused deferment of prophylactic cranial irradiation or consolidative thoracic RT, decide on a case-by-case basis.
Head and neck	1 wk (~10 Gy) of RT, followed by a 2-3 wk break or longer	High	The tumor impact of the initial 10 Gy is essentially lost. Deliver the full prescription dose of 60-70 Gy without reduction once the patient is able to resume therapy.[21]
	Received more than a few weeks of treatment, followed by a treatment interruption	High	Consider accelerated and/or hyperfractionated schedules to try and maintain the overall total treatment time.[21]
	Received substantial radiation dose and then an extended treatment break (on the order of months)	Very High	Surgical salvage. If not feasible, consider full-dose reirradiation despite the known higher risk for late-normal tissue toxicity. In this challenging situation, only treating the gross disease while avoiding elective regions is warranted.[21]
Uterine cervix	Definitive	High	Consider adding approximately 5 Gy per wk with 3-dimensional image-based brachytherapy for each week of radiation duration beyond 7 weeks, respecting the organ-at-risk tolerance doses. This must be carefully weighed against the doses that the organs at risk will receive by adding this extra dose to the tumor.[34] For a 2-3 week interruption, strive for a minimum of 50.4 Gy instead of 45 Gy to the pelvis. Do not recommend twice a day or other altered schedule (weekend or otherwise). Do not discount any previously given dose. The use of LDR instead of HDR brachytherapy would eliminate any need for electricity. If HDR is available only, the physician can admit the patient to the hospital and administer multiple sequential HDR treatments up to twice a day to complete the therapy in a shorter period of time. Use of 4 fractions of 700 cGy rather than 5 fractions of 500-600 cGy can also be considered. Starting the

(*continued on next page*)

Cancer	Clinical scenario	Impact of gap	Recommendations
			brachytherapy during the course of external beam is feasible,[35] but external beam should not be given on the same day as brachytherapy. No treatment break should be given between external beam and brachytherapy.
B	Postoperative	Moderate	Consider adjuvant vaginal cylinder brachytherapy.
Breast	Breast-only treatment	Low	Do not change the whole-breast dose in the setting of a treatment break (continue the original 42.56 Gy in 16 fractions or 50 Gy in 25 fractions). The boost portion of the treatment dose gets adjusted as follows: • Initial treatment plan did not include a sequential boost to the lumpectomy cavity PTV: 10 Gy in 5 fractions boost. • Initial treatment plan included a sequential boost to the lumpectomy cavity PTV: Add one 2 Gy fraction per week missed up to 66 Gy; alternatively, a 2.3 Gy × 5 boost. If the intended boost was to 66 Gy, increase the dose up to 70 Gy, and consider reducing the volume to the highest risk region.
	Chest wall after mastectomy	Low	Similar to above, but substitute lumpectomy cavity PTV for mastectomy scar PTV.
	Regional nodal (supraclavicular, axillary, internal mammary chain) with breast or chest wall	Low	Dose is adjusted to a maximum of 50 Gy in 2 Gy fractions.

Prostate	Very low	For treatment delays <1 wk, no need for corrective action. ADT may safely mitigate delays up to 2 weeks. For patients receiving RT alone for whom a long break is anticipated, consider starting ADT. For patients not undergoing ADT, 1-2 conventional fractions may compensate for a 1-wk break if normal tissue tolerance allows. Accelerating treatment to 6 fractions per wk (1 twice-daily treatment per wk) or switching to a moderately hypofractionated course may help compensate for treatment gaps.[23] When hypofractionating, maintain an equal or slightly higher EQD2 for the tumor using an α/β ratio of 1.5 without exceeding the EQD2 of normal tissues using an α/β ratio of 3.

Abbreviations: ADT = androgen deprivation therapy; EQD2 = equivalent dose in 2 Gy; HDR = high dose rate; LDR = low dose rate; NSCLC = non-small cell lung cancer; PCOC = Prepare, Communicate, Operate, Compensate; PTV = planning target volume; RT = radiation therapy; SCLC = small cell lung cancer.

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