Please note: The purpose of this public consultation is to gather feedback on the content of the guidance.

Following approval of the content, the final document will be professionally proofread, formatted, and designed in accordance with the standard RCR guidance template.

DRAFT FOR CONSULTATION: Management of unscheduled radiotherapy treatment interruptions – RCR Guidance. (Fifth edition)

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Executive Summary

Why radiotherapy treatment interruptions matter

Radiotherapy plays a key role in curing many cancers. To cure cancer with radiotherapy, every tumour stem cell must be eradicated, including those generated during treatment through ongoing cell division.[1] As treatment duration increases, more stem cells can repopulate, reducing the likelihood of local control or cure—especially in fast growing tumours. [2 3 4 5 6 7 8 9 10] Therefore, keeping the overall treatment time as short as possible is critical.

Evidence shows that even a single day of unscheduled interruption can reduce local control by up to 1.4%, with longer delays having a greater impact. [11 12] This applies to those receiving radical primary radiotherapy as well as those being treated with radical postoperative radiotherapy, [13 14] chemoradiotherapy[15 16], and those being treated with combined brachytherapy and external beam therapy, [17 18 19 20 21 22] where overall treatment time is the time for the combined therapy.

Although the volume of published evidence for the effects of treatment prolongation on outcome – particularly for rare or slow growing tumours - is small, it is reasonable to assume that any interruption may negatively affect outcomes. [23 24 25 26] To mitigate these risks, the ASARA principle—"as short as reasonably achievable" —should be applied to any unavoidable interruptions. [27] Whilst this guidance categorises patients into three groups in order of prioritisation, there is no known safe threshold for treatment gaps.

Interruptions should be avoided, and compensatory measures implemented when they occur.

What causes treatment interruptions and the impact of RCR guidance

Past audits by the Royal College of Radiologists (RCR) have shown that treatment interruptions can be significantly reduced through adherence to national guidance and local protocols. In 2000, 60% of patients receiving radical radiotherapy for head and neck cancer experienced interruptions, with only 69% completing treatment within two days of the planned schedule. Causes included public holidays, equipment breakdowns, and patient-related issues. [28] By 2005, after implementing the earlier edition of this RCR guidance, 95% of patients completed treatment within two days, and 88% within one day of the intended overall time. [29 30] Centres with bank holiday working policies showed better compliance and outcomes. These results highlight the importance of robust departmental protocols and regular audits.

About this edition

This RCR guidance now forms the standard of care for patients receiving radical radiotherapy, with each new edition accounting for new evidence, new radiotherapy techniques and modalities.

This fifth edition of this guidance reflects recent developments in clinical practice and radiotherapy delivery including:

- Guidance on managing unscheduled interruptions in hypofractionated breast radiotherapy.
- Reclassification of bladder cancer as a category 1 tumour.

- Additional considerations for compensating gaps using twice-daily treatments.
- Updated real-world case examples of radiobiological compensation to support clinical decision-making.
- Guidance on timing of adjuvant radiotherapy and definitive radiotherapy after neoadjuvant treatment.

It replaces the fourth edition (*The timely delivery of radical radiotherapy: guidelines for the management of unscheduled treatment interruptions fourth edition)* published in 2019.

Key recommendations

General considerations

- Breaks in radiotherapy treatments, especially when given with radical intent, should be avoided where possible, to minimise the adverse effect on local tumour control.
- Interruptions should be kept to a minimum and should adhere to the ASARA (as short as reasonably achievable) principle.
- Sufficient funding should be included in all service delivery contracts to ensure that adequate facilities are available to guarantee continuity of treatment for patients receiving radical radiotherapy. Departmental budgets must have provision to cover overtime payments at weekends or public holidays.

Patient prioritisation on treatment

- Patients should be prioritised for radiotherapy treatment according to their Category, 1, 2, or 3, where the three categories are defined by treatment intent and by tumour type.

Cause and prevention of interruptions

- Departments should take preventative measures to ensure minimum disruption is caused by the major causes of unscheduled interruptions to radical radiotherapy which include:
    - Machine and staff availability
    - Public holidays
    - Transport problems
    - Medical problems
    - Social circumstances that lead to a patient's failure to attend for treatment as scheduled.
- Those responsible for managing the radiotherapy service should carefully consider the impact of machine servicing and quality assurance on the continuity of patients' treatment as well as ensuring the provision of adequate resources in terms of machines and staff.
- Patient transport should be organised to ensure the continuity of treatment.
- Clinical oncologists should ensure that intercurrent illness and psychosocial issues affecting patients, as well as acute toxicities, are optimally managed to minimise the risk of radiotherapy treatment interruptions.
- Radiotherapy services should optimise communication channels with their users.

Management of unavoidable or unscheduled interruptions to minimise impact

- Departments should compensate appropriately for unscheduled treatment interruptions and have local protocols describing this, including Bank holiday working and hyperfractionation as appropriate.
- The ideal procedure is to transfer all patients to a matched linear accelerator on the day of interruption. Where this is not possible, alternative compensatory options include:
    - Weekend treatment, while ensuring that complex treatments can be safely delivered out of normal hours.
    - Twice daily treatment, with a minimum of six hours between treatments
    - Use of biologically equivalent dose (BED) calculations to derive an alternative schedule involving a modified number of treatment fractions with which to complete the radiotherapy course in the planned overall time, but perhaps accepting a higher BED in normal tissues.[31]

- The addition of extra treatment fractions where compensation cannot be achieved within the original overall planned time

Audit and Quality Assurance

- Where unscheduled interruptions occur, each radical prescription should be prospectively reviewed to ensure that the prescriber's intention will be delivered, with the most clinical appropriate compensatory measure chosen.
- Departments should audit the incidence of unscheduled interruptions regularly.

1. Introduction

Who is this guidance for

This guidance is aimed at supporting radiotherapy teams to manage radiotherapy treatment interruptions effectively.

Radiographers identify patients whose radiotherapy treatments have been interrupted and physics staff estimate what changes in treatment are necessary to compensate for the anticipated prolongation. The consultant clinical oncologist will make the final decision regarding what changes are implemented after consulting the radiotherapy team and considering both short and long term impact on patients.

Scope and purpose of the guidance

This guidance outlines best practice for maintaining continuity in radical radiotherapy treatment.

It responds to concerns about the negative impact of unscheduled interruptions and should be embedded in local departmental protocols for effective implementation.

This document is designed to assist clinical oncology departments to achieve this by identifying:

- Which categories of patients are most at risk of loss of tumour control/cure rates from unscheduled interruptions
- The causes of unscheduled treatment interruptions
- How such interruptions in treatment may be prevented
- How to manage unavoidable interruptions to minimise the impact on treatment outcome
- How to evaluate one's service for this.

Grading of recommendations

The types of evidence and the grading of recommendations used within this document are those previously defined by the Scottish Intercollegiate Guidelines Network (SIGN)[32] as specified in Appendix A. Undertaking randomised clinical trials to ascertain the degree of harm caused by treatment delays is clearly not ethical. However, there is strong evidence from multiple clinical series that interruptions increase the risk of local failure, based on poorer outcomes for patients whose radiotherapy is interrupted. The evidence that interruptions cause an increase in the risk of local recurrence is undisputable.[33,34,35,36,37,38]

2. Prioritisation of patients on treatment

Tumours grow at different rates. Even within any one tumour type there will be a wide range of tumour growth rates. Tumour volume doubling time is the most practical way to assess growth rate. The volume doubling time is determined by cell cycle time, growth factor and rate of cell loss. The potential cell doubling time (Tpot) is another means of assessing growth rate and is defined as the time in which the cell population of tumour doubles if there is no cell loss. This is difficult to determine in vivo.

Patients on treatment should be prioritised within the three categories which are defined below. Category 1 tumours tend to have tumours with a relatively short tumour volume doubling time. Those in Category 2 have tumours that have a longer tumour volume doubling time. Both Category 1 & 2 tumours represent those being treated with radical intent, while Category 3 tumours indicate those being treated with palliative intent. Patients on treatment should be prioritised within these three categories.

There is an increasing body of evidence[39 40 41 42 43 44] that unplanned interruptions of radical radiotherapy treatment resulting in prolongation of overall treatment time detrimentally affect local control and cure rates for patients with certain tumours.

Recent data suggest that this applies to those receiving:

- Radical primary radiotherapy
- Radical postoperative radiotherapy[45 46]
- Combined brachytherapy and external beam therapy[47 48 49 50 51 52] (the overall treatment time is the time for the combined therapy)
- Chemo/radiotherapy combinations[53 54](the overall treatment time is the time for the combined therapy).

2.1 Category 1

These are patients with rapidly growing tumours being treated with radical intent. Ideally, treatment duration should not be prolonged over the original prescription. Should this be unavoidable, compensatory measures should be employed.

2.1.1 External beam radiotherapy

Patients with the following tumours should not have their radical radiotherapy prolonged:

- Squamous cell carcinoma of the head and neck region [55 56 57 58 59] (grade B recommendation based on level 2++evidence)
- Non-small cell lung carcinoma (NSCLC) [60 61 62 63 64] (grade C recommendation)
- Squamous cell carcinoma of the cervix[65 66 67 68 69 70 71 72 73] (grade D recommendation)
- Small cell lung carcinoma [74 75] (chemoradiotherapy) (grade D recommendation)
- Squamous cell carcinoma of oesophagus [76 77 78 79] (grade D recommendation)
- Squamous cell carcinoma of skin, vagina or vulva (grade D recommendation)
- Squamous cell carcinoma of the anus [80 81 82 83] (grade A recommendation)
- Adenocarcinoma of the oesophagus [84] (grade D recommendation)
- Medulloblastoma and other CNS embryonal tumours [85 86 87 88] (grade B recommendation based on level 2++ evidence)
- Glioblastoma, especially IDH-wildtype, MGMT methylated [89 90 91 92] (grade C recommendation)
- Intracranial ependymoma[93] (grade D recommendation)

- Carcinoma of the bladder [94] [95] [96] [97] (grade C recommendation).
- Patients with tumours with a short mass-doubling time[98] (grade D recommendation based on level 4 evidence).

It is usually assumed that the outcome for patients with any fast-growing tumour will be adversely affected by treatment interruptions, even in cases where there is no direct evidence. Glioblastomas are very fast-growing tumours, and there is evidence that delay in starting therapy affects outcome. However, there are no reports on the effect of breaks in treatment on outcome; additionally, the complexities of repair in the brain make recommendations for compensation strategies more complex.

2.1.2 Combined external beam radiotherapy and brachytherapy

Patients with the following receiving brachytherapy plus external beam therapy should not have the combined overall treatment time prolonged:

- Squamous cell carcinoma of the cervix[99] [100] [101] (grade B recommendation)
- Squamous cell carcinoma of vagina or vulva (grade D recommendation)
- Squamous cell carcinoma of the tongue [102] (grade C recommendation)
- Squamous cell carcinoma of the anus [103] [104] (grade D recommendation).

2.2 Category 2

These are patients with slower growing tumours, usually adenocarcinomas, being treated with radical intent and include all remaining tumours not included above in section 2.1. Radiotherapy treatment interruptions of more than five days in these patients are detrimental to both local control and survival.[105] [106]No safe lower limit has been established and it is recommended that - where possible - treatment should not be prolonged more than two days. Some form of compensation should be considered where the interruption results in a prolongation of overall treatment time of more than five days. For example:

- ***Breast***: There is some evidence about prolongation of standard courses of radiotherapy for breast cancer.[107] (grade C recommendation).
    - For a 1-week schedule of treatment, there is no evidence to recommend additional dose to compensate for treatment interruptions during 1-week schedules of treatment. Additional hypofractionated doses may result in higher late normal tissue toxicity without evidence of a gain in tumour control. [108] [109] It is recommended that – where possible – treatment should be completed within 3 weeks.
    - For a 3-week schedule, it is not recommend to exceed an overall treatment time of 5 weeks so depending on the length of the gap, dose compensation may need to be considered. [110]
- ***Prostate***: Patients with carcinoma of the prostate[111] [112] [113] [114] (grade D recommendation).

2.2 Category 3

These are patients being treated with palliative intent.[115] Palliative treatment schedules are administered to alleviate symptoms or to obtain local tumour control. Overall time is less critical in achieving the desired palliative outcomes. Prolongation of these schedules may reduce the effect desired and/or the duration of benefit, for example, the management of cord compression and superior vena cava obstruction (SVCO).

The mechanisms for unscheduled treatment extension compensation are the same as for radical therapy. In this situation, there is greater scope for hypofractionation, provided that tissue tolerances are respected. The clinical situation will determine whether a correction is needed but would usually be recommended if the prolongation exceeded seven days.

> Prioritisation of patients on treatment – **key recommendations:**
>
> Three groups are proposed when prioritising patients according to the need to manage interruptions. The distinction between the three categories is determined by tumour type and treatment intent:
>
> **Category 1:** These are patients with rapidly growing tumours being treated with radical intent.
> Treatment duration should not be prolonged over the duration of the original prescription and where unavoidable, compensatory measures should be employed. Treatment must not be prolonged by more than two days over the original prescription for more than 95% of this group.
>
> **Category 2:** These are patients with slower growing tumours being treated with radical intent. Treatment duration should not be prolonged by more than two days over the original prescription; however, prolongation of 5 days may not affect outcome. Some form of compensation should be introduced where the interruption results in a prolongation of overall treatment time of more than five days.
>
> **Category 3**: These are patients being treated with palliative intent. Prolonged interruptions may require compensation, particularly if longer than seven days.

2.4 Recommendations for timing of adjuvant radiotherapy

When radiotherapy is not the first definitive treatment, the timing of subsequent radiotherapy remains important and needs to be considered in the context of clinical benefit across the entire patient pathway. The data supporting specific recommendations for radiotherapy timing after the first definitive treatment is as follows:

Tumour site	Recommendation	Level of evidence
Breast	The risk of local recurrence increases as the interval between surgery and radiotherapy lengthens. The rise in the local recurrence rate may translate into reduced survival. The optimal timings for starting post-operative radiotherapy should be up to 8 weeks after surgery, although up to 20 weeks are acceptable[116].	Level 3, Grade A
Bladder	Adjuvant radiotherapy post cystectomy has only recently come in as a treatment paradigm. There is no data on optimum timing. Trial	Level D

	protocols advocate commencing within 4-10 weeks of cystectomy or within 6 weeks of adjuvant chemotherapy completion[117 118]. On this basis aiming to start with 4-10 weeks of surgery is recommended or as soon as the patient is fit enough	
Central Nervous System	In adult (age ≥ 18) Glioblastoma, adjuvant chemoradiation ideally should start not later than 42 days from surgery, with inconsistent evidence on whether an earlier start improves overall survival[119 120]. In standard risk Medulloblastoma, an interval of more than 7 weeks from surgery to start of radiotherapy has been associated with worse event free survival[121]. In paediatric and young adult ependymoma, no difference in 3-year overall survival was observed in patients starting radiotherapy less than 5, 5-8 or >8 weeks after surgery.	Grade C Grade D Grade C
Gynaecology	In endometrial cancer outcomes appear to be improved if adjuvant radiotherapy commences within 8 weeks of surgery[122 123], though some series suggest shorter intervals and some longer.[124] NCCN guidance recommends starting radiotherapy within 12 weeks.[125] The American brachytherapy Society recommends 4 weeks is left for healing before vaginal brachytherapy commences. [126] For vulva cancer NCCN guidance recommends starting EBRT within 6-8 weeks of surgery as long as wounds healed[127]	
Head and neck	In head & neck cancer, adjuvant radiotherapy should ideally start within 6 weeks of surgery, particularly for high risk patients (positive resection margins, extra-nodal extension). A prolonged interval between surgery and post-operative radiotherapy is associated with significantly reduced locoregional control and overall survival rates[128 129 130].	Level 1, Grade A

Lower GI	Adjuvant radiotherapy in rectal cancer is offered primarily for patients with an R1 resection. In MRC CR07 the median time from surgery to the start of chemoradiotherapy was 57 days (interquartile range (IQR) 43 to 72 days)[131]. There is no evidence investigating the impact of treating outside of this timeframe.	Evidence not available
Lung	Post-operative radiotherapy (PORT) for lung cancer is offered primarily for R1 resection, with limited recommendations for the timing of PORT, as often PORT is given after adjuvant systemic therapy. One retrospective case series suggested the cut-point for optimal PORT should be ≤ 145 days. [132]A further retrospective series suggested that for high-risk patients (N2 disease, poor differentiation, pneumonectomy), optimal timing of PORT is 120-140 days after surgery[133].	Level 3 grade C
Prostate	N/A	N/A
Upper GI	Adjuvant radiotherapy is not routinely indicated in upper GI cancers. Most cases start with chemotherapy unless contraindicated	Evidence not available
Paediatrics	**Medulloblastoma** – the standard recommendation is for radiotherapy to commence within 4-6 weeks after surgical resection. This window allows for postoperative recovery and treatment planning, including molecular risk stratification. A retrospective review of 1338 patients identified from the US national cancer database found initiation of radiotherapy within 3 weeks of surgery to be associated with inferior 5 year survival on multivariate analysis. The same study found no adverse impact when radiotherapy started longer than 5 weeks from, but within 90 days of surgery. The authors therefore concluded that it is reasonable to initiate radiotherapy up to 8 weeks following surgery if clinically necessary to allow for	

	wound healing, resolution of pseudomenngocele and access to optimal management including proton beam therapy.[134 135] However, the aim should be to start within 6 weeks whenever possible. For patients <16 years of age at diagnosis, with R0 (<1.5cm^2 residuum), M0 WNT group medulloblastomas, receiving treatment de-intensification with a craniospinal dose of 18Gy in 10 once daily fractions (as per the PNET5 trial), radiotherapy should start within 28 days of surgery (with an absolute maximum of 40 days)[136]. The total duration of radiotherapy for medulloblastoma should be ideally be less than 45 days. Prolongation beyond this adversely affects tumour control[137]. **Ependymoma** – the standard recommendation is to commence within 6 weeks of surgery although this is based on little clinical evidence. Starting within 8 weeks of surgery may therefore be acceptable in selected cases, to allow for post operative recovery and access to optimal treatment including proton beam therapy[138]. There is evidence to suggest that starting radiotherapy less than 31 days post surgery may confer a higher risk of post radiotherapy imaging changes[139].	

2.5 Recommendations for timing of definitive treatment in the context of neoadjuvant treatment

The data supporting specific recommendations for optimal timing of definitive treatment, be that radiotherapy or surgery after neoadjuvant treatment is as follows:

Tumour site	Recommendation	Level of evidence
Breast	Not commonly used in this setting	
Bladder	Data in patients undergoing cystectomy have reported worse outcomes in people having a longer delay after diagnosis and after	Level D

	neoadjuvant chemotherapy with two studies suggesting inferior cause specific survival for delays longer than 10-11 weeks after chemotherapy. As a result starting treatment between 4-8 weeks after chemotherapy would allow chemotherapy toxicity to recover but avoid significant delay and minimise repopulation and is recommended in most protocols as optimal time periods. The recent RAIDER trial mandated treatment to start within 10 weeks of neoadjuvant chemotherapy completion[140].	
Central Nervous System	N/A	
Gynaecology	Not commonly used in this setting	Evidence not available
Head and neck	N/A – Studies of induction chemotherapy (IC) followed by definitive (chemo)radiation (RT) have not examined the optimal timing of RT after IC[141] [142]. The MACH-NC[143] meta-analysis concluded that concomitant chemotherapy with radiation is superior to IC followed by [C]RT so neoadjuvant SACT is not routine practice in locally advanced HNSCC	Evidence not available
Lower GI	Short course radiotherapy (SCRT) and immediate surgery: Aim is within 1 week of completion of SCRT. Median time to surgery in Stockholm 3 and MRC CR07 was 8 days (IQR 7–10)[144] and 4 days (IQR 3–6) respectively,[145] SCRT and delay / Long course chemoradiotherapy (LCRT): If patients are for surgery, suggested timeframe from (chemo)radiotherapy to surgery is 9-12 weeks, to optimise pathological complete response and sphincter preservation[146] [147]. There are trials ongoing to assess whether the finding of increased surgical morbidity in patients with a timeframe of >11 weeks in GRECCAR 6[148] is maintained in a contemporaneous cohort.[149]. If patients are aiming for organ preservation, surgery at later timelines may be relevant and appropriate anytime in their follow	

	up dependant on ongoing MRI and endoscopic investigations. Total neoadjuvant therapy (TNT) with LCRT first: In OPRA study,[150] chemotherapy was planned to start 3-4 weeks after completion of chemoradiotherapy (CRT). In CAO/ARO/AIO – 12, chemotherapy was planned to start 2-3 weeks after completion of CRT [151].. Neither trial reported actual timing. TNT with LCRT second: In PRODIGE 23 trial radiotherapy was planned to start 1–3 weeks after the last FOLFIRINOX cycle. Trial did not report actual timing.[152] TNT with SCRT first RAPIDO trial suggested an optimal starting time of chemotherapy, 11–18 days after the last day of radiotherapy. Trial reported median time 14 days (IQR 12–17).[153]	
Lung	No role for neoadjuvant systemic therapy prior to definitive cCRT No outcome data available for the optimal timing of definitive surgery after neoadjuvant or perioperative systemic therapy, but the clinical trials (Checkmate 816; Keynote 671; Aegean; NeoADAURA) required surgery be delivered either within 12-20 weeks of the first cycle of systemic therapy or within 6 weeks or 40 days of the last cycle of neoadjuvant therapy.[154] [155] [156] [157]	Not outcome evidence available
Prostate	In prostate cancer, neoadjuvant (NA) androgen deprivation therapy (ADT) is sometimes used before radical radiotherapy (RT), depending on the risk categorisation.[158] [159] The timeframe of when RT starts after commencing ADT is variable in clinical practice and NICE do not have recommendations on this.[159] More recent evidence suggests that NA short-term ADT could be detrimental to progression-free	Level 1, Grade A Level 2-3, Grade B

	survival and metastasis-free survival compared to a concurrent/adjuvant ADT approach with ≥ 2 months adjuvant ADT.[160] [161] Intermediate risk patients (if given ADT): Maximum time to complete RT 6 months. Delays in radiotherapy beyond this can extend the duration of ADT and lead to an increased risk of ADT-related side-effects and affect patient QOL. High risk patients: RT ideally within 6 months, maximum 12 months.[162]	Level 3-4, Grade C-D Level 3, Grade C
Upper GI	There is insufficient evidence to define a recommended interval for definitive radiotherapy following neoadjuvant treatment in upper GI cancers.	Evidence not available
Paediatrics	**Wilms tumour** – early post operative radiotherapy has been shown to have a significant impact on tumour related outcomes. It is currently recommended that radiotherapy commences within 14 days of surgery [163]. **Neuroblastoma** – for intermediate risk neuroblastoma, the LINES protocol[164] recommends initiation of radiotherapy 21 - 42 days post surgery; for high risk neuroblastoma, the HR-NBL2 protocol[165] recommends starting radiotherapy 60-90 days following high dose chemotherapy and autologous stem cell rescue to allow for count recovery. **Parameningeal rhabdomyosarcoma** – local therapy with definitive radiotherapy should commence at week 13 (around the 5th cycle of chemotherapy), Earlier initiation of radiotherapy at around week 4-6 may be considered for higher risk scenarios such as the presence of intracranial extension. In patients with metastatic disease, definitive radiotherapy to the primary disease may be given at week 13 or delayed until weeks 20 – 22 with	

	radiotherapy to sites of metastatic disease if indicated.[166] **Ewing sarcoma** – evidence suggests a possible impact of timing of definitive radiotherapy on local control[167]. Standard recommendation is to commence definitive radiotherapy after cycle 9 of chemotherapy and avoid additional delays.	

3. Causes and prevention of treatment interruptions

The major causes of unscheduled interruptions to radical radiotherapy include:

- Machine and staff availability
- Public holidays
- Transport issues
- Medical problems
- Social circumstances that lead to a patient's failure to attend for treatment as scheduled.

These recommendations focus on preventative measures to avoid treatment interruptions and ensure continuity of patient care.

3.1 Machines and staff availability

- Radiotherapy centres should ensure at least two fully staffed and operational linear accelerators are available at all times, either onsite or through a nearby centre with clear transfer arrangements. [168]
- To maintain uninterrupted patient care, departments should manage machine servicing and quality assurance (QA) efficiently—typically requiring 10–15 working days annually and schedule these activities during weekends or out of hours if patient transfer is not possible.
- Sufficient resources should be in place to allow patient transfers to matched machines during interruptions, especially for advanced techniques, where multiple designated machines are essential (grade D recommendation based on level 4 evidence). If only one machine is available for a specific technique, treatment should be converted to a conventional plan rather than delayed.
- To minimise disruption from machine breakdowns, departments should maintain strong engineering support and ensure rapid access to replacement parts.
- Contingency plans must prioritise patient transfers over cancellations, with agreements in place for prolonged outages.
- For patients receiving both external beam and brachytherapy, even minor delays should be corrected, with at least one weekly brachytherapy theatre list and backup options available. Treatments should be coordinated to limit delays to no more than 1–2 days (grade D recommendation based on level 4 evidence). However, for Category 1 squamous cell gynaecological malignancies, the overall treatment time should not exceed 56 days.[169, 170, 171, 172, 173, 174]
- Adequate staffing - radiographers, physicists, dosimetrists, and engineers—must meet national standards, and departments should aim to reduce weekend breaks in treatment courses, for example starting on a Monday (grade D recommendation based on level 4 evidence). At least one staff member should have the ability to understand and perform radiobiological calculations or have access to this expertise.

3.2 Public holidays

- Departments should aim to treat all patients on public holidays to avoid such disruptions (grade D recommendation based on level 4 evidence), prioritising Category 1 patients if full service is not possible and considering Category 2 patients if two or more consecutive treatment days would be missed.

- Adequate staffing should be arranged to operate radiotherapy units on most, if not all, bank holidays, and essential support services such as transport and hospital operations must also be available.

3.3 Transport issues

- Radiotherapy departments should maintain strong communication with local ambulance and volunteer car services, establishing special arrangements to support twice-daily or weekend treatments when needed.
- An efficient booking system should link treatment machines, transport, and servicing schedules to ensure smooth coordination (grade D recommendation based on level 4 evidence).
- For patients travelling long distances, on-site or hostel accommodation should be offered, and appropriate transport options must be available to support outpatient attendance.

3.4 Medical problems

- Interruptions to radiotherapy caused by intercurrent illness or acute radiation reactions [175] must be minimised through proactive management and support.
- Early intervention by clinical nurse specialists and review radiographers, along with access to drop-in clinics, helps address symptoms before they disrupt treatment.
- Providing patients with written guidance at the start of therapy supports early recognition and management of side effects (grade A recommendation based on level 1+ evidence)
- Additionally, departments should ensure that patients who develop or are at risk of developing medical or psychological issues during treatment can be admitted promptly to avoid delays.

3.5 Psychosocial circumstances leading to a failure to attend for treatment

- Patients should be clearly informed—ideally in writing—about the importance of daily attendance for radiotherapy before treatment begins.
- To help reduce the risk of missed appointments, psychological and social work support should be offered to patients and their families as needed [176] (grade D recommendation based on level 4 evidence).

3.6 Communication

- Referring hospitals and patients should be provided with clear information about the importance of uninterrupted radiotherapy treatment. Patients should receive written guidance on this no later than their planning appointment.
- To support continuity, departments should use patient-specific reminders—such as prompts in electronic prescribing systems or case record proformas—and ensure clinicians are aware of any expected treatment interruptions so they can plan appropriate remedial actions in advance.

Causes and prevention of treatment interruptions: key recommendations

- Departments should take preventative measures to ensure minimum disruption is caused by the major causes of unscheduled interruptions to radical radiotherapy which include:
    - Machine and staff availability
    - Public holidays
    - Transport problems
    - Medical problems
    - Social circumstances that lead to a patient's failure to attend for treatment as scheduled.
- Those responsible for managing the radiotherapy service should carefully consider the impact of machine servicing and quality assurance on the continuity of patients' treatment as well as ensuring the provision of adequate resources in terms of machines and staff.
- Patient transport should be organised to ensure the continuity of treatment.
- Clinical oncologists should ensure that intercurrent illness and psychosocial issues affecting patients, as well as acute toxicities, are optimally managed to minimise the risk of radiotherapy treatment interruptions.
- Radiotherapy services should optimise communication channels with their users

4. Management of unavoidable or unscheduled interruptions to minimise impact

4.1 Transfer to a second machine

Refer to section 3.1 *[link will be added to section 3.1]*

4.2 Accelerated scheduling

- When treatment has been interrupted unexpectedly by only a few days, the scheduled treatment time might be maintained by treating the patient over the weekend.
- Departmental policies should ensure the safety and quality of weekend treatment. Attempts to treat routine patients using protocols developed for emergency weekend cover would be unsafe.
- An alternative is to treat twice daily on some of the other days remaining between the interruption and the end of treatment. Transport restrictions and the lack of day facilities may make this difficult. Where such an approach is possible, the time between the treatments should be a minimum of six hours.[177] [178]
- Consider caution with twice daily treatment with EBRT when fraction size is significantly greater than 2.2.Gy. Where this needs to be considered, for example vulval SIB, ensure peer consultant colleague consensus.
- Twice-daily treatment is also not recommended on a day that concurrent chemotherapy is given if chemotherapy is given at greater than daily intervals and/or if dose per fraction is greater than 1.5Gy.
- Carefully consider twice-daily fractionation as a method of compensation when critical CNS organs at risk are already planned to be treated to tolerance in the initial plan. There is evidence of incomplete repair of late-responding normal tissues even after a six hour interval.[179] [180] [181]

4.3 Biological allowance and radiobiology support

- If an interruption occurs late in the course of radiotherapy for whatever reason, it may be impossible to compensate for the gap in treatment by an accelerated method as described in Section [add details of section], in which case it will be necessary to increase the total dose and/or dose per fraction. This will require the use of radiobiological-based calculations. It should be stressed that these should only be adopted when other methods of compensation cannot be applied. In these cases, assumptions need to be made for parameter values, particularly in tumours which have greater variation than late responding tissues. There are circumstances where this will require a model-based estimate of the correction, as discussed by Dale et al.[182]
- Centres should ensure calculation of biological corrections are carried out by appropriately trained physicists or clinicians.
- A national resource for checking or advising on radiobiological calculations would also be helpful and could be organised as an e-network; such a service could also advise on compensation for over- and underdosage in radiotherapy.

4.4 Increasing the total dose

- Where accelerated scheduling and biological allowance is not possible sometimes the total dose may need to be increased to compensate for the lengthening of treatment time according K factors. [183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193]

4.5 Compensating for other types of radiotherapy: stereotactic ablative radiotherapy (SABR), proton beam therapy (PBT) and superficial radiotherapy

<u>SABR</u>

- There are currently insufficient clinical data to reliably estimate the effects that SABR treatment delays might have on tumour control. It has been hypothesised that giving SABR on non- consecutive days allows for tumour reoxygenation and may actually improve the efficacy of treatment. [194]
- There is limited evidence but in one publication the use of daily lung SABR fractions increased the frequency of ≥ grade 2 toxicities. [195] Given the typical short total treatment times (< 2-3 weeks) accelerated scheduling is therefore not usually indicated patients receiving SABR, and treatment on non-consecutive days should resume after any unintended treatment delays. If there is a prolonged delay, daily fractionation can be considered on an individual case basis based on the risk versus benefits. [196]

<u>PBT</u>

- In general, the principles for PBT are the same as for photon treatments.[197]

<u>Superficial X-ray</u>

- Some Category 1 SCC patients may be treated using kilovoltage treatment units, for which there is usually only one in a department. These treatments are often high dose per fraction (>=5Gy), so are not suitable for twice daily treatment compensation.
- However, they are also often treated less than daily (for example two to three times a week) so any missed treatments can typically be made up on remaining days. Intra-operative or electronic brachytherapy devices used in theatres are usually single fraction, so are outside of scope of this review.

Management of unavoidable or unscheduled interruptions to minimise impact – key recommendations

- Departments should compensate appropriately for unscheduled treatment interruptions and have local protocols to compensate for these, including Bank holiday working and hyperfractionation as appropriate.
- The ideal procedure is to transfer all patients to a matched linear accelerator on the day of interruption. Where this is not possible, alternative compensatory options include:
    - Weekend treatment, while ensuring that complex treatments can be safely delivered out of normal hours.
    - Twice daily treatment, with a minimum of six hours between treatments
    - Use of biologically equivalent dose (BED) calculations to derive an alternative schedule involving a modified number of treatment fractions with which to complete the radiotherapy course in the planned overall time, but perhaps accepting a higher BED in normal tissues.[198]
    - The addition of extra treatment fractions where compensation cannot be achieved within the original overall planned time

5. Audit and Quality Assurance

- It is strongly recommended that radiotherapy departments regularly audit the incidence of unscheduled radical radiotherapy treatment interruptions. Ideally, this should be correlated with outcome to determine if there are other tumour types affected by unscheduled prolongation of treatment time, which should be incorporated into Category 1.
- Any computerised radiotherapy management system should incorporate software to allow a standard audit of this aspect of delivery of treatment.
- Radiotherapy departments are encouraged to interrogate National Radiotherapy Data Set (RTDS) and NATCAN data to benchmark their service against national standards.
- The Australian Clinical Indicator Service Manual for Radiation Oncology (version 5)[199] recommends establishing the planned duration of all Category 1 patients at the outset and auditing any prolongation of more than two days. A similar registry of all Category 1 patients should be developed in UK, to support learning at local and national level.
- Departments should monitor operation of the local protocol and introduce modifications where necessary and ensure there is a designated person in each department to monitor the frequency of interruptions arising in treatments, determine their cause and develop procedures to prevent their occurrence.

Audit and Quality Assurance – key recommendations:

- Where unscheduled interruptions occur, each radical prescription should be prospectively reviewed to ensure that the prescriber's intention will be delivered, with the most clinical appropriate compensatory measure chosen.
- Departments should be audit the incidence of unscheduled interruptions regularly.

6. Further considerations

6.1 Teaching

Teaching in radiation oncology should formally address the issue of unscheduled treatment interruptions and a strong case can be made for national courses at a higher level to ensure more uniform standards.

6.2 Governance

Responsibilities associated with the introduction of biologically corrected doses

- The correction of unscheduled interruptions in therapy results in a change in the patient's proposed therapy.
- Where the patient is transferred to a second machine or is treated on a weekend day, it should not be necessary to alter the consent form. It should however be remembered that the introduction of twice-daily treatment as a means to compensate may have an effect on tumour control and long-term morbidity, so should be discussed with the patient.

Changes in treatment

- The adoption of a biological correction will alter the treatment schedule and may affect outcomes in terms of cure and morbidity. In keeping with Ionising Radiation (Medical Exposure) Regulations (IR(ME)R) guidelines, changes in the management of the patient – fractionation, dose schedule – must be authorised and justified by the practitioner, usually the consultant.[200]
- All clinical decisions regarding changes in therapy should be discussed with the patient and properly documented. The patient should re-consent once the changes have been agreed with the physics staff or appropriately trained operator if the clinician feels that the outcome or side-effects may be altered considerably.

Glossary

Radical radiotherapy refers to treatment courses which use radiation doses that take surrounding tissues up to, or close to, normal tissue tolerance. These are usually curative in nature and include the following:

- Definitive radiotherapy - refers to treatment courses given to patients with potentially curable tumours that are either unresectable or where the evidence base is equivalent for resection and radiotherapy. Chemotherapy may be given alongside this depending on the tumour type and stage.
- Combined brachytherapy and external beam therapy - refers to treatment courses given to potentially curable tumours that are unresectable using a combination of external beam radiotherapy and brachytherapy boost, such as in gynaecological and prostate cancers.
- Adjuvant radiotherapy - refers to treatment courses given after surgery to decrease the risk of recurrence. Chemotherapy may be given alongside this depending on the tumour type and stage.

Palliative radiotherapy refers to treatment courses that use lower radiation doses aiming for symptom control and/or disease shrinkage and are generally recommended for less fit patients or those with distant metastatic disease.

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Appendix 1 Historical background (taken from previous editions of the guidance)

How often do interruptions arise in radiotherapy centres and why?

Reports[1,2,3,4,5,6,7] in the 1980s and 1990s revealed that more than 30% of radical treatments to patients with squamous cell carcinomas (SCC) of the head and neck region were interrupted. The most common causes were public holidays, machine service time, equipment breakdown and patient related issues.[8,9,10] The audit of head and neck cancer in 2005 from the RCR showed that 63% of patients had one or more treatment interruptions.[11] However, with the introduction of local protocols from the guidelines,[12,13] compensation was applied and 88% of interrupted cases completed treatment within one day of target, suggesting a growing awareness of the importance of avoiding treatment interruptions.

Does the length of the interruption matter?

The minimum length of an interruption resulting in prolongation of treatment time that will have a significant effect on local tumour control is difficult to determine, especially when standard departmental treatment times may vary by two days depending upon which day of the week treatment is commenced. Data from split-course therapy studies[3] show that 14–16 day interruptions definitely affect treatment outcome. A relative loss of local control ranging from 3–25% (median 14%) arises when a treatment prolongation of one weekoccurs.[14,15] Mathematical modelling of data from patients with SCC of head and neck, cervix and lung suggests that an unscheduled interruption of one day can, if left uncompensated, result in an absolute reduction of local control of some tumours by 1.0–1.4%.[16,17,24]

A report considering the effect of lengthening combined brachytherapy and external beam therapy in the management of patients with SCC of the tonsil suggested that lengthening the overall treatment time for the combined therapy beyond 42 days significantly reduced local control rates.[18]

For SCC of the anus, data from the large randomised trials have been retrospectively analysed with respect to radiation treatment time, and its correlation with local failure and overall survival. For the Radiation Therapy and Oncology Group (RTOG) trials 87-04 and 98-01, an effect for total (multimodality) treatment time was observed.[19] The ACT2 trial also found a deleterious effect when overall radiotherapy treatment time is increased.[20]

For locally advanced NSCLC there is evidence that radiotherapy delays have a negative effect on overall survival for patients receiving concurrent chemo-radiotherapy. A large retrospective study found there was a significant difference in overall survival (OS) for those patients without delays compared to those with delays (median OS 22.7 versus 18.6 months P<0.0001). In addition, with each cumulative delay, overall survival worsened (standard radiotherapy versus prolonged 1–2 days, 20.5 months, P<0.009; prolonged 3–5 days, 17.9 months, P< 0.0001; prolonged 6–9 days, 17.7 months, P< 0.0001; prolonged >9 days, 17.1 months, P< 0.0001).[21]

Furthermore, the CONCORDE study *[ref to be added*] recommended that the prescribed radiation dose be delivered in 40 days, with consideration of weekend treatment and/or adjustment of fraction size as potential mechanisms of compensating for missed treatments.

In limited stage SCLC treated with concurrent chemotherapy, 45 Gray (Gy) in 30 fractions given twice a day over three weeks, was superior to 45 Gy in 25 fractions given over five weeks for overall survival with a four-month improvement in median overall survival (p=0.04).[22] The CONVERT trial comparing 45 Gy in 30 fractions given twice a day versus 66 Gy in 33 fractions showed a non-significant trend (p=0.14) for improved overall survival in the hyperfractionated arm.[23] In addition, in the CONVERT trial there were strict rules regarding any unplanned treatment gaps to avoid treatment prolongation. These combined results suggest that a shorter overall treatment time is important in SCLC and treatment delays should be compensated for.

For locally advanced cervical cancer, there is evidence that overall treatment time should be as short as possible and should not exceed 56 days for squamous carcinoma.[21,24,25,26,27,28,29]

Adenocarcinoma may respond differently. There are only two reports on breast cancer.[30,38,39]These show that prolongation of more than seven days for those with carcinoma of the breast receiving postoperative irradiation over five weeks results in an increased risk of local recurrence and death.[30,38,39] Analysis of data from the START A and B trials[31] hypothesises that the shorter overall treatment time in the 3-week hypofractionated regimes for adjuvant whole- breast radiotherapy is a significant contributor in maintaining local cancer control. Overall treatment time should therefore be delivered as planned.

Does the timing of the interruption matter?

There is some controversy over whether the timing of the interruption in the treatment schedule is important. The position of an unscheduled interruption does not yet appear to be significant.[1,32,33,34] This may change as more studies are carried out on the data available from meta-analyses.[34,35,36] Accelerated repopulation, which is apparent in some tumour types after 28 days of radiation treatment, alters the K-factor (a factor used to determine the amount of radiation 'wasted' due to ongoing tumour repopulation). Future studies might show that gaps arising in short courses of treatment and gaps arising earlier than 28 days in a long course of therapy have a different effect from interruptions arising later in a long course.

Biological corrections for these events will be different. Correction for interruptions arising later in a long course of therapy is more difficult since it may require the patient to receive a number of large fractions over a short period of time and this is likely to risk increasing long-term late effects.

It has been suggested from animal data using normal pig skin that the day of the week on which an interruption occurs may affect response to radiotherapy.[40] Extrapolating this observation to tumour control would suggest that an interruption on a Monday or Friday which lengthens the weekend break by 33%, may have a more serious adverse effect than an interruption mid-week.[37] Further studies are required to investigate whether such details of the timing of an interruption are important in determining its effect on tumour control in man.

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Appendix 2 The coding for evidence-based recommendations

The types of evidence and the grading of recommendations used within this document are based on those previously proposed by the Scottish Intercollegiate Guidelines Network and utilised effectively in earlier editions of these guidelines.[1]

Recommendation		Evidence	
Grade	**Source**	**Level**	**Type**
A	At least one meta-analysis, systematic review of randomised, controlled trials (RCTs) or RCT rated as 1^{++} and directly applicable to the target population; or a body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population and demonstrating overall consistency of results	1^{++}	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
		1^{+}	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
		1	Meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias.
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated from studies rated as 1^{++} or 1^{+}	2^{++}	High-quality systematic reviews. High-quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
		2^{+}	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
		2	Case control or cohort studies with a high risk of confounding or bias and a significant probability that the relationship is not causal.
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence rated as 2^{++}	3	Non-analytical studies; for example, case reports, case series.
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2^{+}	4	Expert opinion.

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Appendix 3 Worked examples of biological compensation[1]

Recommended format for performing radiobiological compensations

The table below (adapted from Dale et al 2002[2] with small modifications) identifies the main methods for compensation once a gap has occurred and identifies the associated benefits and difficulties.

Method	Benefit	Potential difficulty
1) Retain overall time and dose per fraction by treating on weekend days as necessary.	Overall time, fraction size, interfraction interval and therapeutic index maintained.	May not be feasible for gaps occurring near the end of a schedule.
2) Retain overall time and dose per fraction by treating twice daily as necessary.	Overall time and fraction size maintained.	Possible increase in late-normal tissue damage if many bi-daily fractions have to be used sequentially and/or if the daily interfraction intervals are all less than six hours.
3) Retain overall time by increasing dose per fraction for same number of post-gap days as there were gap days.	Overall time retained by accepting reduced number of fractions. Still utilises one fraction on each treatment day.	Not suitable for schedules which already use high dose per fraction. Therapeutic index adversely affected; that is, seeking equivalence for tumour control gives increase in late reactions. Seeking equivalence for late reactions leads to tumour underdosage.
4) Retain overall time by using smaller number of larger fractions after the gap.	Overall time retained. Still one fraction per day.	As above.
5) Accept that treatment extension is unavoidable and deliver extra fractions, using increased dose per fraction to minimise the extension duration.	Allows at least partial restoration of the prescribed schedule.	Therapeutic index adversely affected. Might require acceptance of both reduced tumour control and increased late effects.
6) As for 5 but use twice-daily fractions and a slightly longer treatment extension.	As above.	As for 5 but deterioration in therapeutic index may not be so marked.

Calculation process

It should be noted that these radiobiological calculations are based on linear-quadratic models with allowances for tumour proliferation. These are best-fit models formulated from experimental data.199 They are very sensitive to tumour and normal tissue α/β values, estimates for which have varied widely when such models are applied to clinical data.

Uncertainties in these inputs will be necessarily reflected in the outputs from these calculations. Nevertheless, they may be applied as a guide to the magnitude of dose correction required to compensate for prolongation in overall treatment time. It is ultimately the responsibility of the individual clinician to select the most appropriate values for the equations.

While each example of a treatment interruption is to some extent unique and will require its own solution, it is possible to adopt a standardised approach to compensation. The suggested method involves concentrating first on the normal tissue BED value in order to identify what can be done to effect compensation without exceeding tolerance. After that, the necessary compromises may be explored and evaluated.

Once an unscheduled gap has occurred, first determine the remaining treatment time and the number of fractions which, according to the prescribed schedule, are still to be delivered. Determine if there are ways of delivering these treatment fractions which would allow the originally prescribed treatment time to be maintained; for example, by treating at weekends or by giving all or part of the remaining treatment twice daily. If this is possible then a radiobiological compensation should not be necessary. (Examples 1 and 2 later in this Appendix relate to such a case.) If this option is not feasible (that is, it is not possible to complete treatment within the prescribed treatment time) then the following steps should be carried out. The relevant equations to be used are listed below:

1. First calculate the normal tissue BED for the prescribed schedule using Eq(A). This calculation should make use of the dose actually received by the critical normal tissue, if this is different from the prescribed tumour dose.
2. Determine the respective pre-gap normal-tissue BED, also using Eq(A).
3. The difference between the BEDs calculated in (1) and (2) determines the late-normal BED 'still to give' (the post-gap BED).
4. Review the various treatment options (such as twice-daily fractionation, hyperfractionation and increased fraction sizes) to ascertain which will be likely to produce the minimum extension to the treatment time, then calculate the required dose per fraction to achieve the required late-normal BED value.
5. For the selected option, calculate the associated tumour BED using Eq(B), remembering to make allowance for the extended time (Examples 3 and 4 below demonstrate different versions of this scenario).
6. Review the final tumour and normal tissue BEDs which will result from the preferred compensation option. If the tumour BED is significantly smaller than that originally prescribed, a degree of clinical judgement may be required in order to 'fine-tune' the compensation to arrive at a reasonable compromise. (Example 4 illustrates the dilemmas which become more critical in such cases.)

It is stressed that these are general steps. For example, if the favoured compensation option involves several closely spaced fractions after the gap, a modified BED formula must be used[3,4] in order to take account of the possible enhancement to normal tissue toxicity as a consequence of incomplete repair. It is suggested that if twice-daily fractions are to be given on two/three or more successive days then the effects of incomplete repair should be considered, especially if brain or spinal tissue is at risk.

Equations

Calculation of normal tissue BED (for well-spaced fractions):

$$\textbf{Eq (A): } BED = Nd \times \left[1 + \frac{d}{\alpha/\beta}\right]$$

where N is the number of (well-spaced) fractions and d the dose per fraction. The recommended generic value of α/β is 3 Gy, the important exception being for spinal cord, for which a value of 2 Gy should be used.

$$\textbf{Eq (B): } \boldsymbol{BED = Nd \times \left[1 + \frac{d}{\alpha/\beta}\right] - K \times \left(T - T_{delay}\right)}$$

Calculation of tumour BED

where T is the overall treatment time and T_{delay} is the time elapsed from the beginning of treatment before the onset of rapid repopulation. K is the daily BED-equivalent (units $Gy \cdot day^{-1}$) of repopulation. The generic tumour α/β value is usually taken to be 10 Gy but there are some exceptions, important examples being breast and prostate cancer.

Further details and worked examples are given by Bentzen *et al*.[4]

WORKED EXAMPLES

Worked examples 1–3 each consider ways of handling five-day gaps. In practice, the majority of unscheduled interruptions will probably involve interruptions of less than five days and are correspondingly easier to deal with. All examples involve a reference schedule of 70 Gy delivered in 35 fractions over 46 days, typically used for Category 1 head and neck tumours. The overall time of 46 days corresponds to a treatment beginning on a Monday, continues with daily fractionation for seven weeks with no treatment at weekends and finishes on a Friday. For a similar 35-fraction schedule which begins mid-week, the treatment time will be longer (because the treatment will extend into an eighth week) and specific calculations should allow for this.
For other schedules, such as the commonly used four-week treatments, the principle involved in determining a method of compensation is exactly the same as set out in the seven-week examples used here. In such cases, however, there is more concern about twice-daily treatments if the dose per fraction is already significantly larger than 2 Gy, because of the greater potential for incomplete repair.

EXAMPLE 1. Loss of all of the third week (five fractions) of a treatment schedule of 70 Gy/35 fractions/46 days

1. **Determine the remaining treatment time and the number of fractions which, according to the prescribed schedule, are still to be delivered.**

Assuming the treatment began on a Monday, the intended overall treatment time is 46 days. After the gap, treatment resumes on the Monday of the fourth week of the schedule. Ten fractions have been delivered; 25 remain to be given.

2. **Determine if there are ways of delivering these treatment fractions which would allow the originally prescribed treatment time to be maintained; for example, by treating at weekends or by giving all or part of the remaining treatment twice daily**

If treatment is to be completed on the prescribed finishing date the available number of days (including weekends) is 26. Thus, the missed dose in the gap can be compensated for by delivering the remainder of the treatment on weekdays (20 fractions) and on five of the six remaining weekend days. This does not involve changing the fraction size and, as the treatment is not extended, constitutes a ‘good’ compensation.

If weekend treatments are not feasible a good compensation is still possible if, on five of the 20 remaining treatment days, two fractions are delivered instead of one. The important proviso is that the twice-daily fractions must be delivered with a minimum time gap between them of six hours. It is further recommended that the days on which twice-daily treatments are delivered are not consecutive but spaced throughout the available time period. In this instance, Fridays are a good choice for delivery of some of the twice-daily fractions as there is a greater opportunity for completion of repair before treatment resumes the following week. In cases where the individual fraction sizes are appreciably greater than 2 Gy, particular care needs to be taken with the use of bi-daily fractionation since the issue of interfraction spacing and the distribution of the bi-daily treatment days throughout the remaining schedule becomes more critical.

EXAMPLE 2. Loss of all of the sixth week (five fractions) of a treatment schedule of 70 Gy/35 fractions/46 days

1. **Determine the remaining treatment time and the number of fractions which, according to the prescribed schedule, are still to be delivered.**

After the gap, treatment resumes on the Monday of the seventh week of the schedule. Twenty-five fractions have been delivered and N=10 remain to be given.

2. **Determine if there are ways of delivering these treatment fractions which would allow the originally prescribed treatment time to be maintained; for example, by treating at weekends or by giving all or part of the remaining treatment twice daily**

Ideally these ten fractions should be delivered over the five remaining treatment days so as not to extend the treatment. The missed dose can therefore be compensated for by delivering the remainder of the treatment as twice-daily fractions (minimum of six hours apart) in each weekday of the final week. This does not involve changing the fraction size and, as the treatment is not extended, constitutes a good compensation.

A better solution, if feasible, would be also to make use of the weekend before the final week of treatment, thus providing seven days within which ten fractions have to be delivered. Bi-daily fractionation could be used, for example, on Monday, Wednesday and Friday, single fractions on the other four days. The advantage of the latter scheme is that it reduces the likelihood of creating excess normal tissue damage in the event that there is incomplete repair between fractions.

Examples 1 and 2 do not involve changing fraction size or overall time and, provided there is reasonable spacing between treatment days on which bi-daily treatment is given, do not invoke any quantitative evaluations or serious radiobiological dilemmas. The following examples illustrate the compromises involved in more difficult cases.

EXAMPLE 3. Loss of all of the seventh week (five fractions) of a treatment schedule of 70 Gy/35 fractions/46 days

1. **Determine the remaining treatment time and the number of fractions which, according to the prescribed schedule, are still to be delivered.**

In this example, the unscheduled gap extends to the time when treatment should have finished. There are N=5 fractions to be delivered.

2. Determine if there are ways of delivering these treatment fractions which would allow the originally prescribed treatment time to be maintained; for example, by treating at weekends or by giving all or part of the remaining treatment twice daily.

In this case any form of compensation will extend the treatment time beyond the scheduled time. It is, therefore, necessary to use calculations to first determine how much normal tissue BED there is ‘still to give’ after the gap.

3. First calculate the normal tissue BED for the prescribed schedule using Eq(A). This calculation should make use of the dose actually received by the critical normal tissue, if this is different from the prescribed tumour dose. The recommended generic value of α/β is 3 Gy, the important exception being for spinal cord, for which a value of 2 Gy should be used.

For the prescribed treatment the normal tissue BED (BED_3) is, from Eq(A):

BED3Gy = 35 x 2 x [1 + (2/3] = 116.7Gy

4. Determine the respective pre-gap normal-tissue BED, also using Eq(A).

BED3Gy = 30 x 2 x [1 + (2/3] = 100Gy

5. The difference between the BEDs calculated in (1) and (2) determines the late-normal BED ‘still to give’ (the post-gap BED).

The allowable BED_3 left to give without increasing tolerance is therefore

BED3Gy “still to give” = 116.7 – 100 = 16.7 Gy_3.

6. Review the various treatment options (such as twice-daily fractionation, hyperfractionation and increased fraction sizes) to ascertain which will be likely to produce the minimum extension to the treatment time

- We begin by assuming that the missing dose is replaced by treating with five 2 Gy fractions over a full extra (eighth) week, beginning on a Monday. On completion, the overall time is seven days longer than scheduled. With a daily BED-equivalent of tumour repopulation of 0.9 Gy·day–1, the tumour BED10 will be lower than intended by an amount 7 × 0.9 = 6.3 Gy10, that is, it will be reduced to 67.8 – 6.3 = 61.5 Gy_{10}, a fall of over 9%. The late normal BED_3 will be as originally prescribed.
- If instead, the outstanding daily treatments are given in the period Saturday–Wednesday, the net treatment extension is five days; that is, the tumour BED_{10} is reduced by 5 × 0.9 = 4.5 Gy_{10} (6.6%).
- A further alternative is to treat two fractions per day on Saturday and Monday with one fraction on Sunday, thus extending treatment by only three days. In this case, the tumour BED10 will be lowered by an even smaller amount of 3 × 0.9 = 2.7 Gy10 (4%). In each of these instances, the normal tissue BED_3 will again be as prescribed.

7. For the selected option, calculate the associated tumour BED using Eq(B), remembering to make allowance for the extended time.

The tumour BED (BED_{10}) for the prescribed schedule is, using Eq(B) with K = 0.9 and Tdelay = 28 days:

Prescribed tumour BED10Gy = 35 x 2 x [1 + (2/10)] – [(46--38) x 0.9] = 67.8Gy

The dilemmas arise when attempts are made to increase the total dose to restore the tumour BED_{10} to that originally intended; in this case it is impossible to do so without increasing the normal tissue BED_3 beyond that originally prescribed. Delivering extra doses by treating with extra fractions has the effect of further extending the treatment time, which may compound the original problem. Increasing the dose per fraction helps offset the deleterious influence of the treatment extension but, because of the greater sensitivity of the late-responding critical tissue to changes in dose per fraction, will increase the normal tissue BED proportionately more than that for the tumour.

We next consider an instance where it is felt essential to restore the tumour BED_{10} to what it should be, initially without regard for the effect on the normal tissue. We assume the option of treating additionally over the weekend is to be adopted, taking the overall time to 46 + 5 = 51 days.

The tumour BED10 of 67.8 Gy10 is to be maintained. Therefore, for the whole schedule (pre- gap plus post-gap):

BED10 (pre-gap) + BED10 (post-gap) – tumour repopulation factor = prescribed BED10 where d is the new value of dose per fraction to be utilised over the five fractions. The solution for d in the above equation is d = 2.62 Gy; that is, 5 × 2.62 Gy will restore the tumour BED_{10} to that initially prescribed. Again, it should be noted that the required extra BED_{10} of (5× 0.9 =) 4.5 Gy_{10} cannot be added simply pro rata across the five 2 Gy fractions. The values of the biological Gy_{10} and the physical Gy units are different, and they cannot be added; to do so would lead to an even higher fraction dose of 2.9 Gy.

8. **Review the final tumour and normal tissue BEDs which will result from the preferred compensation option. If the tumour BED is significantly smaller than that originally prescribed, a degree of clinical judgement may be required in order to 'fine-tune' the compensation to arrive at a reasonable compromise.**

For the normal tissue, the compensated treatment increases the BED_3 to: BED3 (pre-gap) + BED3 (post-gap), that is:

$$100 + 5 \times 2.62 \times \left[1 + \frac{2.62}{3}\right] = 124.5\ \mathrm{Gy}_3$$

Thus, the revised treatment delivers a 6.7% excess in normal tissue BED_3. To evaluate what this compensated scheme would mean in terms of the equivalent dose in a schedule delivered with 2 Gy fractions we note that, by re-arrangement of Eq(A):

$$\textit{Total dose in 2 Gy fractions} \times \left[1 + \frac{2}{3}\right] = 124.5$$

The total dose in 2 Gy fractions would be 74.7 Gy. Thus, the given normal tissue BED_3 is approximately equivalent to just over 37 × 2 Gy fractions.

If this is considered to be excessive it is possible to 'split the difference', that is, aim to achieve a tumour BED_{10} which is a little less than that prescribed while accepting a small increase in normal tissue BED_3. Such a result may be arrived at by trial-and-error processing of different values of dose per fraction. For instance, in the above example an intermediate dose per fraction of 2.3 Gy would deliver a total tumour BED_{10} of:

BED10 (pre-gap) + BED10 (post-gap) – tumour repopulation factor:

$$30 \times 2 \times \left[1 + \frac{2}{10}\right] + 5 \times 2.3 \times \left[1 + \frac{2.3}{10}\right] - (51 - 28) \times 0.9$$

$$= 65.4\ \mathrm{Gy}_{10}$$

$$30 \times 2 \times \left[1 + \frac{2}{10}\right] + 5 \times d \times \left[1 + \frac{d}{10}\right] - (51 - 28) \times 0.9 = 67.8\ \mathrm{Gy}_{10}$$

The normal tissue BED is:

BED3 (pre-gap) + BED3 (post-gap):

$$30 \times 2 \times \left[1 + \frac{2}{3}\right] + 5 \times 2.3 \times \left[1 + \frac{2.3}{3}\right] = 120.3\ \mathrm{Gy}_3$$

Thus, with 2.3 Gy fractions in the compensation, the tumour and normal tissue BEDs are respectively 3.5% lower and 3.1% higher than for the uninterrupted schedule. The effects of alternative values of dose per fraction could be tested, as appropriate, using the same process. It is stressed that the process of hypofractionating treatment after the gap is not necessarily the best option: a better result is likely to be obtained if some extra fractions can be used (via bi-daily fractionation) in order to restrict use of excessive fraction size.

WORKED EXAMPLE FOR A MORE COMPLEX CASE

Unscheduled interruptions of longer than five days are generally more difficult to deal with as there is less chance of completing treatment without incurring a significant extension of the treatment time. The following example highlights such cases.

EXAMPLE 4. Loss of all of the sixth and seventh weeks (ten fractions) of a treatment schedule of 70 Gy/35 fractions/46 days

1. **Determine the remaining treatment time and the number of fractions which, according to the prescribed schedule, are still to be delivered.**

As in Example 3, the unscheduled gap runs right up to the time when treatment should have finished. In this case however, a very significant part of the treatment has yet to be delivered. In order to minimise the consequent extension to treatment time it is inevitable that an increased dose per fraction will need to be considered if treatment is to be delivered in once-daily fractions.

2. **Determine if there are ways of delivering these treatment fractions which would allow the originally prescribed treatment time to be maintained; for example, by treating at weekends or by giving all or part of the remaining treatment twice daily**
    - We initially attempt to complete treatment in five fractions delivered during the eighth week – the treatment time is extended by seven days to 53 days. We first aim to match the prescribed late-normal tissue BED_3 (116.7 Gy_3), that is, the dose per fraction to use is d, where d is solved from:

BED3 (pre-gap) + BED3 (post-gap) = Required BED3 that is: for which d = 3.22 Gy

This same dose per fraction would produce a resultant tumour BED_{10} of:

BED10 (pre-gap) + BED10 (post-gap) – tumour repopulation factor:

$$25 \times 2 \left[1 + \frac{2}{10}\right] + 5 \times 3.22 \times \left[1 + \frac{3.22}{10}\right] - (53 - 28) \times 0.9 = 58.8\ \mathrm{Gy}_{10}$$

$$25 \times 2 \times \left[1 + \frac{2}{10}\right] + 10 \times d \times \left[1 + \frac{d}{10}\right] - (60 - 28) \times 0.9 = 67.8\ \mathrm{Gy}_{10}$$

Thus, despite using a large dose per fraction for the last five fractions, the resultant tumour BED_{10} is still 13.2% less than prescribed.

- If the weekend prior to the eighth treatment week is used for treatment, then seven fractions may be delivered, leading to a fractional dose of 2.57 Gy and a tumour BED_{10} of 60.1 Gy_{10}. If 11 fractions are distributed over the seven available treatment days (by treating bi-daily on four of them) the required fractional dose drops to 1.87 Gy, the tumour BED10 then being 61.9 Gy10. This latter value is still 8.7% short of the prescribed tumour BED10 (67.8 Gy10), thus some degree of compromise, achieved by increasing dose per fraction as illustrated in the previous example, might be considered. In extreme cases, three times-daily fractionation could be considered, but only after careful consideration of the potential for detriment from incomplete repair.
- If weekend or twice-daily fractionation cannot be accommodated, then it might be considered necessary to carry out the remaining treatment over two full working weeks – extending treatment into an eighth and ninth week – making the overall treatment time 46 + 14 = 60 days. For this, the dose per fraction (d) ideally required to maintain the tumour BED_{10} is obtained from:

BED10 (pre-gap) + BED10 (post-gap) – tumour repopulation factor: for which d = 2.85 Gy, leading to an associated BED_3 of 138.9 Gy_3, which is 19% higher than prescribed. This result demonstrates the alternative dilemma associated with further extending the treatment to avoid weekend and twice-daily treatments: the total dose to be delivered is again increased by the extension into the ninth week, with a consequent penalty to BED_3.

WORKED EXAMPLES FOR ALTERNATIVE DOSE FRACTIONATIONS

EXAMPLE 5: Loss of 3# in week 3 in a treatment schedule of 55Gy/ 20# over 4 weeks

1. **Determine the remaining treatment time and the number of fractions which, according to the prescribed schedule, are still to be delivered.**

Assuming the treatment began on a Monday, the intended overall treatment time is 28 days. After the gap, treatment resumes on the Thursday of the third week of the schedule. Ten fractions have been delivered; 10 remain to be given.

2. **Determine if there are ways of delivering these treatment fractions which would allow the originally prescribed treatment time to be maintained; for example, by treating at weekends or by giving all or part of the remaining treatment twice daily**

If treatment is to be completed on the prescribed finishing date the available number of days (including weekends) is 11. Thus, the missed dose in the gap can be compensated for by delivering the remainder of the treatment on weekdays (7 fractions) and on three of the four remaining weekend days.

This does not involve changing the fraction size and, as the treatment is not extended, constitutes a ‘good’ compensation.

If weekend treatments are not feasible a good compensation is still possible if, on three of the 7 remaining treatment days, two fractions are delivered instead of one.

The important proviso is that the twice-daily fractions must be delivered with a minimum time gap between them of six hours. It is further recommended that the days on which twice-daily treatments are delivered are not consecutive but spaced throughout the available time period. In this instance, Fridays are a good choice for delivery of some of the twice-daily fractions as there is a greater opportunity for completion of repair before treatment resumes the following week.

In cases where the individual fraction sizes are appreciably greater than 2 Gy, particular care needs to be taken with the use of bi-daily fractionation since the issue of inter-fraction spacing and the distribution of the bi-daily treatment days throughout the remaining schedule becomes more critical.

EXAMPLE 6: Loss of 3# (or 5#) in week 4 (#16-18, #16-20) of a treatment schedule of 55Gy/20#

1. **Determine the remaining treatment time and the number of fractions which, according to the prescribed schedule, are still to be delivered.**

Assuming the treatment began on a Monday, the intended overall treatment time is 28 days.

- After the 3# gap, treatment resumes on the Thursday of the last week of the schedule. Fifteen fractions have been delivered; 5 remain to be given.
- After the 5# gap, treatment resumes on the Saturday of the last week of the schedule. Fifteen fractions have been delivered; 5 remain to be given.

2. **Determine if there are ways of delivering these treatment fractions which would allow the originally prescribed treatment time to be maintained; for example, by treating at weekends or by giving all or part of the remaining treatment twice daily**

- After the 3# gap, ideally, the 5 remaining fractions should be delivered over the four remaining treatment days (including weekend days) so as not to extend the treatment. The missed dose can therefore be compensated for by delivering the remainder of the treatment as twice-daily fractions (minimum of six hours apart) in at least one day of the four remaining days. This does not involve changing the fraction size and, as the treatment is not extended, constitutes a good compensation.
- After the 5#gap, the 5 remaining fractions can not be delivered in the remaining two days so as not to extend the treatment. Therefore we need to calculate how we will compensate.

3. **First calculate the normal tissue BED for the prescribed schedule using Eq(A). This calculation should make use of the dose actually received by the critical normal tissue, if this is different from the prescribed tumour dose. The recommended generic value of α/β is 3 Gy, the important exception being for spinal cord, for which a value of 2 Gy should be used.**

$BED_{3Gy} = 55 \times [\ 1 + (2.75/3] = 105.42Gy$

4. **Determine the respective pre-gap normal-tissue BED, also using Eq(A).**

BED3Gy = (15x2.75Gy) x [1 + (2.75/3] = 79.06Gy

5. The difference between the BEDs calculated in (1) and (2) determines the late-normal BED 'still to give' (the post-gap BED).

BED3Gy "still to give" = 105.42 – 79.06 = 26.36Gy

6. **Review the various treatment options (such as twice-daily fractionation, hyperfractionation and increased fraction sizes) to ascertain which will be likely to produce the minimum extension to the treatment time**

If we do not treat at the weekend

- Daily at 2.75Gy: 5 days extension

7. For the selected option, calculate the associated tumour BED using Eq(B), remembering to make allowance for the extended time

Prescribed tumour BED10Gy = 55 x [1 + (2.75/10)] – [(35 – 28) x 0.9] = 65.625Gy

BED10Gy (pre-gap) + BED10Gy (post-gap) = Prescribed BED10Gy
(15x2.75Gy) x [1 + (2.75/10)] + (5 x d) x (1 + (d/10)] – [(35 – 28) x 0.9] = 65.625Gy
52.59 + (5 x d) x (1 + (d/10)] – [(35 – 28) x 0.9] = 65.625Gy
(5 x d) x [1 + (d/10)] = 65.625 – 52.59 + 6.3 = 19.64Gy
d= 3.02Gy

The remaining 5 fractions must be delivered at 3.02 Gy daily.

8. Review the final tumour and normal tissue BEDs which will result from the preferred compensation option. If the tumour BED is significantly smaller than that originally prescribed, a degree of clinical judgement may be required in order to 'fine-tune' the compensation to arrive at a reasonable compromise.

For the normal tissue, the compensated treatment increases the BED_3 to: BED_3 (pre-gap) + BED_3 (post-gap), that is:

79.06 + (5x3.02) x [1 + (3.02/3)] = 109.36 Gy
So, the BED3Gy has increased by 114.27 – 109.36 = 4.91 Gy (4.5%)

<u>EXAMPLE 7: Loss of the third week of treatment (5 fractions) of a treatment schedule of 65Gy/30# over 6 weeks</u>

1. Determine the remaining treatment time and the number of fractions which, according to the prescribed schedule, are still to be delivered.

Assuming the treatment began on a Monday, the intended overall treatment time is 40 days. After the gap, treatment resumes on the Monday of the fourth week of the schedule. Ten fractions have been delivered; 20 remain to be given.

2. Determine if there are ways of delivering these treatment fractions which would allow the originally prescribed treatment time to be maintained; for example, by treating at weekends or by giving all or part of the remaining treatment twice daily

If treatment is to be completed on the prescribed finishing date the available number of days (including weekends) is 23. Thus, the missed dose in the gap can be compensated for by

delivering the remainder of the treatment on weekdays (15 fractions) and on 5 of the 8 remaining weekend days.
This does not involve changing the fraction size and, as the treatment is not extended, constitutes a ‘good’ compensation.

EXAMPLE 8: Loss of all of the sixth week of treatment (5 fractions) of a treatment schedule of 65Gy/30# over 6 weeks

1. **Determine the remaining treatment time and the number of fractions which, according to the prescribed schedule, are still to be delivered.**

Assuming the treatment began on a Monday, the intended overall treatment time is 40 days. Twenty-five fractions have been delivered; 5 remain to be given.

2. **Determine if there are ways of delivering these treatment fractions which would allow the originally prescribed treatment time to be maintained; for example, by treating at weekends or by giving all or part of the remaining treatment twice daily**

There are no days left if we are not treating at the weekend.

3. **First calculate the normal tissue BED for the prescribed schedule using Eq(A). This calculation should make use of the dose actually received by the critical normal tissue, if this is different from the prescribed tumour dose. The recommended generic value of α/β is 3 Gy, the important exception being for spinal cord, for which a value of 2 Gy should be used.**

BED3Gy = 65 x [1 + (2.17/3] = 112.02Gy

4. **Determine the respective pre-gap normal-tissue BED, also using Eq(A).**

BED3Gy = (25x2.17Gy) x [1 + (2.17/3] = 93.49Gy

5. **The difference between the BEDs calculated in (1) and (2) determines the late-normal BED ‘still to give’ (the post-gap BED).**

BED3Gy “still to give” = 112.02 – 93.49 = 18.53Gy

6. **Review the various treatment options (such as twice-daily fractionation, hyperfractionation and increased fraction sizes) to ascertain which will be likely to produce the minimum extension to the treatment time**

If we do not treat at the weekend

- Daily at 2.17Gy: 5 days extension

7. **For the selected option, calculate the associated tumour BED using Eq(B), remembering to make allowance for the extended time**

Prescribed tumour BED10Gy = 65 x [1 + (2.17/10)] – [(47-40) x 0.9] = 74.61Gy
BED10Gy (pre-gap) + BED10Gy (post-gap) = Prescribed BED10Gy
(25x2.17Gy) x [1 + (2.17/10)] + (5 x d) x (1 + (d/10)] – [(47-40) x 0.9] = 74.61Gy
66.02 + (5 x d) x (1 + (d/10)] – [(47-40) x 0.9] = 74.61Gy
(5 x d) x [1 + (d/10)] = 74.61-66.02 + 6.3 = 14.89Gy
d= 2.4Gy
The remaining 5 fractions must be delivered at Gy daily.

8. Review the final tumour and normal tissue BEDs which will result from the preferred compensation option. If the tumour BED is significantly smaller than that originally prescribed, a degree of clinical judgement may be required in order to 'fine-tune' the compensation to arrive at a reasonable compromise.

For the normal tissue, the compensated treatment increases the BED_3 to: BED_3 (pre-gap) + BED_3 (post-gap), that is:

93.49 + (5x2.4) x [1 + (2.4/3)] = 115.09Gy
So, the BED3Gy has increased by 115.09 – 100.66 = 14.43Gy (14.3%)

Some further clinical considerations

1. Concurrent chemotherapy schedules will have an associated BED but they will be the same for treatments regardless of gaps. Consequently, no allowance is necessary. However, it would seem prudent not to deliver concomitant chemotherapy on the same day as accelerated compensatory treatments.
2. Maintaining a tumour BED may be considered necessary in some indications, where no salvage therapy is possible. The patient may also have strong views on whether to preserve tumour control and accept higher risks of more serious normal tissue side-effects and the possibility of their subsequent management using surgery and so on. In cases where the risk of a severe normal tissue reaction is high and not amenable to surgical or other correction (such as spinal myelitis) then a more conservative approach would be favoured.
3. Where feasible, field size reductions can be used in the later stages of compensation therapy to minimise the normal tissue volume exposed to a higher BED where relevant.
4. A change in the sequence of treatment might be allowed to save a further loss of time: for example, earlier introduction of a Phase 2 boost technique is possible in some instances (medulloblastoma, breast,) depending on the circumstances. If external beam treatment is poorly tolerated, use of a slightly higher dose of a more focal form of radiotherapy such as brachytherapy might be indicated.
5. In cases where it is technically not possible to perform a treatment such as brachytherapy following a course of external beam treatment, the use of chemotherapy in the enforced gap should be considered.

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