RCR
The Royal College of Radiologists

The timely delivery of radical radiotherapy: standards and guidelines for the management of unscheduled treatment interruptions, Third edition, 2008

Board of Faculty of Clinical Oncology
The Royal College of Radiologists

Contents

Foreword

Radiotherapy is involved in the care of 40% of those patients who are cured of their malignancy.[1] The details of the delivery of a radiotherapy prescription are critical to its success. The Royal College of Radiologists (RCR) has published documents on:

- Conformal radiotherapy planning[2] (2002)
- Devolved radiotherapy centres[3] (2004)
- Radiotherapy dose fractionation[4] (2006)
- Audits of waiting times for treatment[5] (2006)
- Geometric verification of treatment[6] (2008).

These documents together set quality standards for radiotherapy, but, to be fully effective, treatment must be delivered in the prescribed overall time.

Good clinical practice demands that radical courses of radiotherapy should not be interrupted. Prolongation of any radiotherapy treatment may adversely affect patient outcome.

This document gives guidance on identifying the factors that cause interruptions, how to compensate for them and sets standards for the timely delivery of radical radiotherapy in order to assure the best outcomes for patients.

The first edition of *Guidelines for the Management of the Unscheduled Interruption or Prolongation of a Radical Course of Radiotherapy*[7] was published by the RCR in 1996. The second edition[8] of the document updated the advice issued in 1996, and took into account the results of a national audit conducted in 2001[9] under the auspices of the Audit Sub-Committee of the Board of the Faculty of Clinical Oncology.

It is hoped that this third edition will be helpful to departments of clinical oncology in producing local protocols to minimise the impact of unscheduled interruptions in radiotherapy treatment and thus achieve the best possible outcomes for patients.

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Executive summary

Good clinical practice dictates that radical courses of radiotherapy treatment should not be interrupted. Where this is not possible, compensatory treatment is required.

For a wide range of fast-growing tumours, there is extensive evidence that uncompensated interruptions to radiotherapy, resulting in prolongation of overall treatment time, increases the risk of local recurrence of these tumours.[10] This applies not only to those receiving radical primary radiotherapy but also to those being treated with radical postoperative radiotherapy,[11] chemoradiotherapy and those being treated with combined brachytherapy and external beam therapy,[12–15] where overall treatment time is the time for the combined therapy. Mathematical modelling of the data from various studies suggests that an unscheduled gap of one day can result in an absolute reduction of local control by 1.4%.[16] A separate clinical study reported that a prolongation of overall treatment time by two days when treating patients with laryngeal tumours over four weeks significantly affected treatment outcome.[17]

The effect of treatment prolongation has not been investigated in all fast-growing tumours and there have only been a few studies into the effect of interruptions on the outcome of treatment for patients with slow-growing tumours. However, in keeping with good clinical practice, it is to be expected that any interruption to radiotherapy schedules may affect outcome.

Although the published evidence for the effects of treatment prolongation on outcome is small, it must be appreciated that the rules of evidence-based medicine[18] were intended for use in evaluating the benefits of therapeutic interventions. They were not proposed for evaluating the risks of exposure to potentially avoidable hazards. Although we have categorised patients into three groups, there is no theoretical reason to state that there is any threshold below which an interruption is safe. We recommend that steps be taken to prevent any interruptions in therapy. In situations where they arise, we recommend the adoption of Mackillop's ASARA principle that interruptions should be As Short As Reasonably Achievable.[19]

Patient categorisation

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 one patients

These are patients with rapidly growing tumours, such as squamous carcinomas, being treated with radical intent. The effects of interruptions on the outcomes of such cancers have been assessed by a number of international studies.[20,21] Treatment duration must not be prolonged by more than two days over the original prescription.

Category two patients

These are patients with slower growing tumours, usually adenocarcinomas, being treated with radical intent. There are reports that prolongation of five days may not always be deleterious,[22,23] but no safe minimum has been established. It is advised that their treatment should not be prolonged by more than two days over the original prescription.

Category three patients

These are patients being treated with palliative intent. Overall time is less critical in achieving the desired palliative outcomes. Prolonged interruptions, which may occur because of intercurrent illness, may require compensation, particularly if longer than seven days.

Service provision

This document describes in detail the steps which departments should take to deliver a satisfactory service for their patients and defines acceptable standards of care.

Departments must establish robust systems of service planning, according to local protocols, to cope with predictable and unpredictable interruptions to normal treatment.

Planning the overall service

- Working across bank holidays to prevent interruption to patients' treatment must become the norm.
- The impact of machine servicing and quality assurance on the continuity of patients' treatment must be carefully considered in scheduling these activities.
- The provision of adequate resources in terms of machines, staff and training must be the subject of long-term planning.
- Patient transport must be organised to ensure continuity of treatment.

Management of unavoidable/unforeseen or unscheduled interruptions

Such episodes may arise as a result of machine breakdown, staff or patient illness. The following measures are recommended for the management of any potential interruption in treatment or prolongation of time schedules.

- The ideal procedure is to transfer all patients to a matched linear accelerator on the day of interruption.

  Where this is not possible the following approaches are recommended.
  - Where possible, there should be the facility which allows patients who have missed scheduled weekday treatments due to machine failure, illness, and so on to be treated at the weekend. A special departmental protocol must be introduced to ensure that complex treatments can be safely delivered out of normal hours.
  - Patients can be treated twice daily, with a minimum of six hours between therapies[24] – in principle, this approach is best used towards the end of a week to allow more repair of sub-lethal damage to normal tissue over the ensuing weekend.
  - 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.[25]
  - The addition of extra treatment fractions where compensation cannot be achieved within the original overall planned time.
- Each radical prescription should be prospectively reviewed to ensure that the prescriber's intention will be delivered.

1 Introduction

Radiotherapy is an important modality in the management of patients with cancer. It is involved in treating 40% of those who are cured.[1] To achieve cure of a patient with cancer, radiotherapy must eradicate every tumour stem cell.[26]

All the stem cells associated with the tumour plus any additional stem cells generated during the course of treatment by continuing cell division must be included in the target volume.[27] The probability of eradicating a cancer with a given dose of radiation is inversely related to the number of stem cells present in the treatment volume.[28]

The rate of cell division varies widely among similar tumours and different tumour types.[29–31] The longer a course of treatment, the more stem cells can repopulate, increasing the number of stem cells that have to be obliterated. As overall treatment time increases, the probability of local control cure by radiotherapy decreases. Those cancers which show rapid cellular repopulation will be less likely to be cured when the overall treatment time is extended.[32]

This document represents the response of the RCR to concern about the potential adverse effects of unscheduled treatment interruptions on outcomes for patients receiving a radical course of radiotherapy.

The types of evidence and the grading of recommendations used within this document are those defined by the Scottish Intercollegiate Guidelines Network (SIGN)[33] as specified in Appendix A. However, it must be appreciated that the rules of evidence-based medicine[18] were intended for use in evaluating the benefits of therapeutic interventions. They were not proposed for evaluating the risks of exposure to potentially avoidable hazards. Sackett recommends a different approach to the evaluation of the potential harms of treatment which is much closer to the approach generally used in evaluating environmental hazards.[18] Recognising that it is usually unethical to do randomised, clinical trials purely to evaluate potential harm to patients, Sackett recommends that in appraising evidence in this context, we begin by asking the question, 'Was the type of study done the strongest that could have been performed under the circumstances?' He then recommends that Hill's criteria for cause and effect relationships are applied to the entire body of evidence that bears on the question.[34] There is strong evidence that interruptions increase the risk of local failure, based on worse outcomes for patients whose radiotherapy is interrupted. The evidence that interruptions cause an increase in the risk of local recurrence is unassailable, at least for fast-growing squamous carcinomata of the context of head and neck.[16,20,21,35–37] These findings are strongly supported by robust radiobiological theory, which has been validated experimentally.[38]

A recent review of the quality of evidence and the strength of recommendations[39] drew attention to the four key determinants of the strength of a recommendation: first, the balance between desirable and undesirable consequences of alternative management strategies; second, the quality of the evidence; third, the relative uncertainty about patient preferences; and finally, cost. Evidence continues to accumulate highlighting the fact that uncompensated interruptions in radiotherapy disadvantage the patient and increase the risk of local recurrence and death from cancer. In this document the quality of evidence for statements is explicitly presented. It is clear that there is no reason for most patients to want an interruption to their recommended radiotherapy as it risks compromising the chance of cure. There will be a cost in providing adequate provision to compensate for interruptions but this will be offset by the savings in sparing recurrence. Overall, radiotherapy has been shown to be a remarkably cost-effective service.[40–43]

This document sets standards for the continuity of a course of radical radiotherapy. It specifies evidence-based categorisation of patients according to their tumour type. The evidence relating to the effect of prolongation of overall treatment time on therapy outcome for patients with tumours arising at various sites is based on cohort studies,[20,21,35,44,45] mainly on fast-growing squamous tumours of head and neck.

The effect of treatment prolongation has not been investigated on all fast-growing tumours. Some cancers are too rare to permit an accumulation of such evidence and for them we have to rely on expert opinion; this forms a small minority of our recommendations.

There have only been a few studies into the effect of interruptions on the outcome of treatment for patients with slower growing tumours. However, in keeping with good clinical practice, interruptions to radiotherapy schedules in the management of this group should also be minimised, as it is to be expected that they will affect outcome.

The patients are categorised into three groups, but there is no theoretical reason to state that there is any threshold below which an interruption for those placed in category two is safe. We recommend that steps be taken to prevent and minimise any interruptions in therapy. In situations where they arise we recommend the adoption of Mackillop's ASARA principle that interruptions should be As Short As Reasonably Achievable.[19]

The document discusses ways of overcoming interruptions to treatment. Some of these are based on radiobiological models which have been developed over the past 30 years. Consideration has been made to the position of the 'gap' a) in relation to the day of the week and b) in relation to the time of the start of therapy. In these situations, it has been necessary to extrapolate data from animal and laboratory studies to draw some conclusion.[46]

The implementation of these national guidelines will be best achieved if they are developed locally into departmental protocols. 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.

The guidelines highlight the role of the consultant clinical oncologist in the decision process. The identification of patients whose radiotherapy treatments have been interrupted and the estimation of what changes in treatment are necessary to compensate for the anticipated prolongation are usually carried out by radiographers and physics staff respectively. The final decision regarding what changes in therapy are implemented depends on the consultant clinical oncologist. S/he will interact with radiographers, physics staff and clinical nurse specialists and then make a decision after considering what effect the proposed changes will have on the patient in question both in the short and long term.

This publication updates the Second Edition[8] which is now withdrawn.

2 Background

2.1 Introduction

'Conventional' radical fractionation schedules evolved to accommodate the standard working practice of weekend breaks and are considered to compensate empirically for tumour repopulation during the non-treatment days. The addition of further interruptions to the planned schedule, which potentially result in prolongation of overall treatment time, will affect outcome.

2.2 How often do interruptions arise in radiotherapy centres and why?

Reports[17,44,37,48–52] 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. This was an international phenomenon (Table 1). The Scottish Radiological Society undertook a prospective audit of patients with laryngeal tumours receiving radical radiotherapy.[44] They found that 34% of patients were treated within the prescribed time, 29% had their treatment prolonged by one or two days and 37% had a longer interruption (3–15 days). The audit of head and neck cancer in 2005 from the RCR[53] shows that 63% of patients had one or more treatment interruptions. However, with the introduction of local protocols from the guidelines,[7,8] compensation was applied and 88% of interrupted cases completed treatment within one day of target. The cause of an interruption cannot always be specified. This probably reflects the lack of general awareness of the importance of avoiding treatment interruptions. Reported causes of interrupted schedules are listed in Table 2, and advice on their management is given in Section 4.

The data in Table 2 highlights that most gaps are due to logistics (50– 83%) and few are patient related.

Table 1. Frequency of prolongation of radical treatments for patients with SCC of the head and neck

		Treatment lengthened	Treatment lengthened	Treatment lengthened
Series	**Patients (n)**	**by 1–5 days**	**by 6–10 days**	**by >10 days**
RTO[48]			36%	22%
Louisville[49]	104		49%	24%
*Aarhus1[50]	181	52%	29%	19%
*Aarhus2[51]	93		45%	22%
*Aarhus3[52]	51		4%	4%
Dresden[45]	192	48%		24%
		Treatment lengthened	Treatment lengthened	Treatment lengthened
		by 3–7 days	**by 8–14 days**	**by >14 days**
Gliwice[37]	971	33%	34%	10%
SRS[44]	96	91%	8%	1%

* Aarhus took action in Series 3 to prevent the interruptions recorded in Series 1 and Series 2, and actively compensated whenever possible by treating twice a day

Table 2. Causes of treatment interruptions from three surveys

	1994[44]	2000[9]	2005[53]
Department-related			
Planned			
Public holidays/statutory days	46%	–	39%
Machine service time	31%	37%	35%
Unplanned	7%	–	–
Machine breakdown	–	13%	9%
Patient-related			
Radiotherapy reactions	16%	8%	8%
Patient unwillingness	–	5%	4%
Unspecified	–	37%	5%
Total	100%	100%	100%

2.3 Therapies and tumour types

There is an increasing body of evidence[10,16,20,21,35,36] 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[11,54]
- Combined brachytherapy and external beam therapy.[12–14,55,56] (The overall treatment time is the time for the combined therapy)
- Chemo/radiotherapy combinations.[56,57] (The overall treatment time is the time for the combined therapy).

The tumour types reported in the literature as being most affected by interruptions include:

- Head and neck squamous cell carcinomas (HNSCC)[21,38,58]
- Cancers of the cervix[55,59–63]
- Cancers of the lung: a) non-small cell (NSCLC)[57,64–66] and b) small cell (SCLC)[56,67]
- Cancers of the oesophagus[68–71]
- Medulloblastoma and primitive neuroectodermal tumours (PNET).[72–74]

The mechanism is likely to be repopulation of tumour clonogens due to either a de novo high proliferating fraction or accelerated repopulation occurring in response to anti-neoplastic treatment.

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.[75,76] However, there are no reports on the effect on breaks in treatment on outcome; additionally, the complexities of repair in the brain make recommendations for compensation strategies more complex.

There is more uncertainty regarding transitional carcinoma of the bladder.[77–80] Two small reports[78,79] suggested that prolonging treatment of patients with bladder cancer might affect outcome, but two larger retrospective studies from Holland and Belgium showed no significant effect of prolonging treatment time on outcome.[77,80]

The biological behaviour of slower growing tumour types is such that it has been reported that a prolongation of five days does not significantly affect patient outcome – local control and survival – as determined by statistical analysis. This would appear to apply to patients with carcinomas of the anus[81–83] receiving chemoradiotherapy. The data for adenocarcinoma of the prostate is inconclusive.[84–87]

For breast cancer, two series have been reported showing an adverse effect on both local control and survival if treatment was prolonged for more than seven (*grade D recommendation*, see Appendix A) days in a five-week course of treatment.[22,23] There are no published data on shorter courses of treatment. We recommend that treatment should not be prolonged more than two days (*grade D recommendation*).

Palliative treatment schedules are administered to alleviate symptoms such as pain, bleeding, or to obtain local tumour control to prevent ulceration. They may also aid healing of ulcers, and reduce tumour mass causing pressure symptoms, and so on. Prolongation of these schedules may reduce the effect achieved and/or 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.[88]

2.4 Does the length of the interruption matter?

The minimum length of an interruption which results 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[45] show that 14–16 day interruptions definitely affect treatment outcome. A relative loss of local control ranging from 3 to 25% (median 14%) arises when a treatment prolongation of one week[36,89] occurs. Mathematical modelling of data from patients with squamous cell carcinomas 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 to 1.4%.[10,15,16]

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.[12]

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.[4,13,14,55,61–63]

Adenocarcinoma may respond differently. There are only two reports on breast cancer.[22,23] 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.[22,23]

2.5 Does the timing of the interruption matter?

There is some controversy over whether the timing of the interruption in the treatment schedule is important.[37] The position of an unscheduled interruption does not yet appear to be significant.[35,37,47,90] This may change as more studies are carried out on the data available from meta-analyses.[91–94] 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 those arising earlier than 28 days in a long course of therapy have a different effect from those 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 may 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.[46] 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.[95] Further studies are required to investigate whether such details of the timing of an interruption is important in determining its effect on tumour control in man.

2.6 The need for departmental protocols

The development and implementation of guidelines for the identification of patients potentially at risk and how to prevent or manage unplanned prolongation of therapy are a health priority. Implementation of such guidelines in local healthcare plans and audit plans has the potential to improve the local tumour control rates in certain tumour types, reducing long-term healthcare costs.

In 2000, the RCR Clinical Oncology Audit Sub-Committee undertook a national audit of the management of interruptions arising in the radical treatment of patients with squamous cell carcinoma of the head and neck attending the 55 cancer centres in the UK.[9] This was repeated in 2005.[53] The audits were based on the first and second editions of the *Guidelines for the Management of the Unscheduled Interruption or Prolongation of a Radical Course of Radiotherapy*.[7,8]

The outcome measures of the audit were:

- Frequency and causes of interruptions to therapy
- Policy and compliance with policy for managing interruptions
- Prolongation
- Time between first visit to clinic and start of treatment.

2.7 Interruption policies

In 2000, seven centres (13%) were unable to introduce any policy due to local circumstances. The remainder adopted one or more of the policies recommended by the RCR.[8] This is confirmed by a recent survey by Dale *et al*.[96]

The RCR reaudit in 2005 showed that the guidelines and the local adoption of policies had improved the delivery of radical radiotherapy schedules. Sixty-three per cent of the 631 patients registered in 2005 by 48 of the 57 centres had one or more treatment interruptions compared to 60% of the 2,553 cases registered in the 2000 audit.[54] However, in 2005, 88% of patients with interruptions completed treatment within one day of target and 95% within two days compared to 69% within two days in 2000.

In 2000, the 48 centres that had incorporated bank holiday working into their policies were able to comply with their policy more often (74% vs 49% of cases) and apply a remedy more often (86% vs 69% of cases) than those centres that did not treat patients on a bank holiday.

2.8 Conclusion

The available data strongly suggest that unscheduled and uncompensated prolongation of radical treatment adversely affects local tumour control in a number of tumour types. For this reason, it is extremely important that each department has its own protocols to compensate for unscheduled interruptions. The longer a gap is, the more damaging is the effect.

Many interruptions are predictable and can be planned for.

3 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 (T_{pot}) is another means of assessing growth rate and is defined as the time 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 defined below. Those with tumours in Category 1 tend to have tumours such as squamous cell carcinomas with a relatively short volume doubling time. Those in Category 2 will have tumours such as adenocarcinomas which have a longer volume doubling time.

3.1 Category 1

Patients with the tumour types for which there is evidence that prolongation of treatment affects outcome, and who are being treated radically with curative intent. The data reviewed[10] show very strong evidence that prolongation of overall treatment time affects treatment outcome or local tumour control (cure rates) in patients with the tumours listed below.

Any audit of this category of patient – departmental or national – should show that there was no prolongation of overall treatment time in excess of two days for at least 95% of the group.

3.1.1 External beam radiotherapy

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

- Squamous cell carcinoma of the head and neck region[9,35,37,38,90] (*grade B recommendation on level 2^{++}evidence*)
- Non-small cell carcinoma of lung (*NSCLC*)[57,64,65,97] (*grade C recommendation*)
- Squamous cell carcinoma of the cervix[13,14,55,59–63] (*grade D recommendation*)
- Small cell carcinoma of lung[56,67] (chemoradiotherapy) (*grade D recommendation*).
- Squamous cell carcinoma oesophagus[68–71] (*grade D recommendation*)
- Squamous cell carcinoma skin, vagina or vulva (*grade D recommendation*)
- Adenocarcinoma oesophagus[69] (*grade D recommendation*)
- Medulloblastoma and primitive neuroectodermal tumours (PNET)[72–74] *(grade B recommendation on level 2++ evidence)*
- Patients with tumours with a short mass doubling time[32] (*grade D recommendation based on level 4 evidence*).

3.1.2 Combined modality radiotherapy

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

- Squamous cell carcinoma of the cervix[14,55,63] (*grade B recommendation*)
- Squamous cell carcinoma of the tongue[12] (*grade C recommendation*).

3.2 Category 2

Patients with slower growing tumour types, who are being treated radically, where interruptions in radiotherapy leading to an extension of overall treatment time of more than five days are detrimental to both local control and survival.[22,23] No safe lower limit has been established, and we recommend that where possible treatment should not be prolonged for more than two days.

Any audit of this category of patient – departmental or national – should show that there was no prolongation of overall treatment time in excess of two days for at least 95% of the group. It is accepted however that a prolongation of five days may not affect outcome in this category of patient.

- Patients with squamous cell carcinoma of the anus[81–83] treated with chemoradiotherapy should not have their radical treatment prolonged by more than seven days (*grade C recommendation*).

- Patients with adenocarcinoma of the breast[22,23] receiving postoperative therapy over five weeks or more should not have their radical treatment prolonged by more than five days (*grade C recommendation*).
- There is no evidence about prolongation of shorter (three-week) courses of radiotherapy for breast cancer. We recommend that treatment should not be prolonged by more than two days (*grade D recommendation*).
- Patients with transitional cell carcinoma of the bladder[77–80] (*grade D recommendation*).
- Patients with carcinoma of the prostate[84–87] (*grade D recommendation*).

Some form of compensation should be introduced where the interruption results in a prolongation of overall treatment time of more than five days.

3.3 Category 3

Patients being treated palliatively.[88] Overall time is less critical in achieving the desired palliative outcomes. Prolongation, which may occur because of intercurrent illness, may require compensation, particularly if longer than seven days.

3.4 Summary

Ideally, there should be no breaks in the delivery of any radiotherapy treatments especially those given with radical intent. If there are adequate facilities in a department there should be no need, except in certain medical situations, for any patient to experience an uncompensated break in treatment.

It is strongly recommended that all patients receiving radical radiotherapy should have the delivery of their treatment schedule audited. 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.

4 Management of potential prolongation of a treatment schedule

4.1 Preventive measures – how can interruptions be avoided?

The five major causes of unscheduled interruptions in a course of radical radiotherapy are:

- 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.

4.1.1 Machine and staff availability

Centres treating patients radically should have ready access to a minimum of two fully staffed and operational linear accelerators at all times, either within the centre or at a second centre situated close by, with clear arrangements for transfer. It is vital that centres can provide continuity of care.

The issues to be dealt with are availability of resources, machine servicing and quality assurance (QA), and how to deal with unplanned down time.

Machine servicing schedules and QA procedures account for ten to 15 working days annually. Each department must make arrangements to ensure that any interruption to patient treatment is minimised by these processes. If patient transfer to a matched machine (see below) is not possible then this work should be carried out during weekends or out of hours. This can be difficult as it puts an added strain on staff groups already working under pressure and suppliers are not always available to provide necessary support at these times.

Ideally, each centre should have sufficient resources compatible with the departmental workload to allow a percentage of patients to be transferred to an alternative, matched machine should an interruption occur (*grade D recommendation based on level 4 evidence*).

On a machine service day, all patients should be transferred to an alternative, matched linear accelerator. If it is not possible to treat patients on a service day, the machines should not be serviced on a Monday or Friday. Individual departmental servicing schedules will depend on local resources such as the number of accelerators, length of working day and departmental staffing arrangements (*grade D recommendation based on level 4 evidence*).

Where departments have adopted new radiotherapy techniques, such as intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT) or stereotaxis, there should be a second designated, matched machine available to allow the patient's treatment to continue uninterrupted (*grade D recommendation based on level 4 evidence*). For those departments with only one machine capable of treating patients with IMRT and so on, in case of breakdown, it is recommended to convert treatment to a conventional plan rather than leave a prolonged gap in treatment.

Machine breakdowns can cause severe disruption even though the uptime of modern accelerators varies between 95% and 98%. Uptime can be maximised by good engineering support either in house or through manufacturers' engineers working under service contracts. There should be robust arrangements for the quick supply of parts for linear accelerators. Centres should have a contingency plan to deal with service interruptions and the system should be flexible to permit transfer of patients on breakdown rather than send them home.

For prolonged interruptions lasting longer than a few days, it might be necessary to agree a contingency plan with another provider to make up any major shortfall. This would be a complex undertaking. The new provider would have to allocate a consultant to act as a practitioner who prescribes the remainder of the treatment. Replanning of patients' treatment will be required unless the linear accelerators involved are compatible. There would also be major issues of staffing. Staff transfer might be difficult, they may not be trained to use the machines at the second site. Transport would have to be arranged.

Where patients are being treated by combined external beam and brachytherapy, corrections should be considered for the smallest of interruptions. There should be at least one brachytherapy theatre list per week with the option of a replacement if there is a loss of a scheduled list. Treatments within the department should be organised so that brachytherapy and external beam therapy can be integrated smoothly so that the overall treatment time is kept to the minimum with a maximum prolongation of 1–2 days (*grade D recommendation based on level 4 evidence*).

Centres must have adequate numbers (at least in line with national recommendations) of radiographers, physicists, dosimetrists and engineering staff.

4.1.2 Public holidays

There are at least seven bank holidays in the UK. It is recognised that interruptions caused by public holidays affect treatment outcome. Ideally all patients should still be treated on public holidays (*grade D recommendation: level 4 evidence*), but this may not be practicable. If this cannot be arranged then at least the treatment of patients in Category 1 should not be stopped on these days. The value of a department having a recognised policy for the management of unscheduled interruptions has been published.[9] Treating on public holidays will have many consequences, including staffing, transport and other hospital support services.

Those in Category 2 may also benefit from being treated similarly, when two or more consecutive treatment days will otherwise be lost.

4.1.3 Transport problems

Every oncology centre must have an efficient means of communication with its local ambulance service and volunteer car service. If it intends to provide twice-daily treatments or weekend treatments as a way to compensate for interruptions, then special arrangements with one or both of these services will have to be established. To facilitate the organisation of treatments, each department should have an efficient booking system which links treatment machines, transport and servicing arrangements (*grade D recommendation based on level 4 evidence*).

4.1.4 Medical problems

Interruption of treatment is sometimes caused by intercurrent disease or as a consequence of acute radiation reactions.[98] Every effort must be made to ensure that these reactions are managed to reduce the risk of treatment delay. This requires proactive support from appropriate healthcare professionals, experienced radiographers, nursing staff, dietitians and so on, to ensure that the reactions are minimised. Written guidance to patients at the start of treatment facilitates the recognition and management of early reactions (*grade A recommendation based on level I^{+} evidence*). Clinical nurse specialists play an important role in the management of these cases and 'drop-in' clinics are beneficial to all patients receiving radiotherapy as they allow patients to have their symptoms treated early, before they become troublesome and lead to interruption of their radiotherapy.

4.1.5 Psychosocial circumstances leading to a failure to attend for treatment

Organising a long, demanding and resource-intensive course of treatment is pointless if the patient is not prepared to co-operate and attend daily for therapy. Patients must be made aware of the importance of daily attendance for treatment, and this should be clearly stated in writing before treatment starts. Psychological and social work support should be given where required to patients and their families.[99] This will help reduce the risk of patients failing to attend (*grade D recommendation based on level 4 evidence*).

5 Compensatory measures

There are a number of procedures that can be adopted to prevent or minimise the effects of prolongation of overall treatment time. One or more should be adopted by each cancer centre and formalised in a departmental protocol.

5.1 Transfer to a second machine

Ideally patients in Category 1, and where possible, those in Category 2, should be treated daily (allowing for normal weekend breaks). If the potential interruption is due to machine unavailability – breakdown or service – patients should be transferred to an alternative, matched machine. This can be done with the minimum of effort within any department if the unit has matched linear accelerators. Departments are encouraged to consider this need when planning new or replacement equipment. Each department should develop its own protocol to allow patient transfer without delay. One means of facilitating this is to prepare contingency plans for an alternative, matched machine at the time of initial planning for radical treatment courses. A service continuity machine allows patients and staff to be moved as required when one linac is down for service or repair.[100]

In any department where patients are being treated by IMRT, IGRT or stereotaxis, two matched linear accelerators should be identified as the treatment machines so that patients can be readily transferred, should the machine they are being treated on be unavailable for therapy. For those departments with only one machine capable of treating patients with IMRT and so on, in case of breakdown, it is recommended to convert treatment to a conventional plan rather than leave a prolonged gap in treatment.

5.2 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. If weekend treatments are to be introduced as department policy then a protocol will have to be prepared. Most departments have arrangements to treat emergency patients on a Saturday and/or Sunday. This emergency cover is usually limited and works to a local protocols. Attempts to treat routine patients using these protocols on an *ad hoc* basis would be unsafe.

A second alternative is to treat twice daily on some of the other days remaining between the interruption and the end of treatment. Where this approach is possible, the time between the treatments should be a minimum of six hours.[24,101] Twice-daily treatment is not recommended when fraction size is significantly greater than 2.2 Gy. Transport and/or the lack of day facilities may make this difficult.

5.3 Biological allowance

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 in described in Section 5.2, 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.*[25]

5.4 Increased total dose

Various analyses have been used to determine by how much the total dose should be increased to compensate for lengthening of the treatment time. Early estimates[16,91,102–109] indicated that head and neck K factors[a] (dose/day, $Gyday^{-1}$) were in the range 0.5–0.74 $Gyday^{-1}$. A K factor is the factor used in standard biologically effective dose (BED; a measure of biological dose delivered to a tumour or organ) calculations to determine the amount of radiation 'wasted' due to ongoing tumour repopulation. This is equivalent to the λ/α factor used in some publications.

More recent and sophisticated analyses of multi-centre data show that K values for head and neck cancer are higher than originally believed. A meta-analysis of data from Edinburgh, Glasgow, Manchester and Toronto[21] estimates the K value to be 0.89 (95% confidence limits, 0.35–1.43) $Gyday^{-1}$. This is supported by the results of the RTOG 9003 head and neck trial[92] and the analyses carried out by Withers[93] and Fowler and Harari[94] who suggest K values of 0.94–0.99 $Gyday^{-1}$. It is important to realise that the selected K value must be viewed in conjunction with the time after the start of treatment at which fast tumour repopulation is assumed to begin. For head and neck cancers, Dale *et al*[25] suggest a working value for K of 0.9 $Gyday^{-1}$, in conjunction with a delay time of 28 days.

6 Implementation

Following the development of local protocols, providers should consider how best to implement and audit their use.[108] Local protocols should be circulated to all relevant staff, and displayed in planning departments and all megavoltage treatment units. These protocols should be included within any departmental treatment guidance and should be incorporated into any quality assurance (QA) standards. One RCR audit[9] has shown that different centres have adopted different strategies to deal with events causing prolongation of radical therapy. There is no evidence that one policy is better than another.[9]

6.1 Availability of resources

Radiotherapy centres providing treatment with radical intent should have ready access to a minimum of two linear accelerators at any time. The RCR is aware of the difficulties that may occur during the times when machines are being replaced and it is essential that treatment standards are maintained during such periods. Centres should have their Linacs matched and linked by a patient management system to allow easy transfer of patients from one machine to another when required.

On-site or hostel accommodation should be available for patients who have to travel long distances to receive their radiotherapy. It should be possible to admit patients who develop or are expected to develop medical or psychological problems during therapy. There must be appropriate transport facilities available for those attending as outpatients. Many areas have volunteer cancer services which will bring patients for therapy. Departments must ensure that they have adequate numbers of staff: radiographers, physicists, dietitians, and so on. Arrangements should be made to ensure that radiotherapy units work normally on most if not all bank holidays.[100]

Each department should ensure that at least one of their staff has the ability to understand and perform radiobiologically based calculations or arrange an alternative way to provide the service.

6.2 Patient-specific reminders at the time of prescription or treatment

These may include pro formas within case records, and tables displayed on megavoltage treatment units showing patient categories. Clinicians prescribing treatments should be made aware of interruptions that may be expected to arise during the planned course of therapy to allow them to agree prospective remedial action when prescribing.

6.3 Communication

Clearly, communication is necessary not just for relevant staff but also for patients. Staff in hospitals referring patients to the centre will also require appropriate information concerning the need for continuity of treatment. Patient understanding of the importance of this issue requires specific written information which should be given no later than the planning appointment.

6.4 Audit

Hospital managers, clinical directors, head radiographers and heads of radiotherapy physics departments, directors of ambulance services, clinicians and many others will want access to data associated with the implementation of these guidelines. Any computerised radiotherapy management system should incorporate software to allow a standard audit of this aspect of delivery of treatment.

6.5 Audit of key outcome indicators

The major outcome indicator following radical radiotherapy is local tumour control. Patients receiving radical radiotherapy should be the subject of regular audit. The possible effect of unscheduled prolongation of treatment on local control should form part of that continuing audit programme. As the collation of cancer outcomes data improves, the development of the Radiotherapy Data Set (RTDS) project will give the opportunity to audit the outcome of radical treatment from each cancer centre and collate it centrally. Analysis of this master database would facilitate a regular review of those tumour types in Category 1. The results of modifying treatment using the biological allowance factors could also be evaluated.

6.6 Quality assurance

As for all QA standards, the operation of the local protocol must be monitored and modifications introduced where necessary.

6.7 Funding

Adequate 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.

6.8 Research

The RCR wishes to encourage research into this important aspect of radiotherapy treatment delivery. Other means of compensating for interruptions could also be investigated.

6.9 Supervision

There should be 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.

6.10 Teaching

It is essential that 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.

6.11 Radiobiology support

Calculation of biological corrections should be carried out by appropriately trained physicists or clinicians: few consider themselves to be expert in these procedures in the UK. Ideally, they should have attended an appropriate course.

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. A recent audit[96] has shown that standards vary and that more external advice is being requested.

7 Governance

7.1 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. Obviously the patient will have to be informed that their appointments with regards to weekend treatments have been altered. It should also be remembered that the introduction of twice-daily treatment as a means to compensate may have an effect on tumour control and the long-term morbidity.

7.2 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)[109] guidelines, changes in the management of the patient – fractionation, dose schedule – must be authorised and justified by the practitioner, usually the consultant. All clinical decisions regarding changes in therapy should be 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.

Appendix A. The coding for evidence-based recommendations

The types of evidence and the grading of recommendations used within this document are based on those proposed by the Scottish Intercollegiate Guidelines Network.[33]

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; eg, case reports, case series
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2^{+}	4	Expert opinion

Appendix B. Worked examples of biological compensation

Recommended format for performing radiobiological compensations

The table below (*adapted from Dale et al 2002,*[25] *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 6h.
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; ie, 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

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 below 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 at the end of this Appendix.)

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 (for example, twice-daily fractionation and hyperfractionation, increased fraction sizes, and so on) 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 3–6 below demonstrate various 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. (Examples 4–6 illustrate 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, the modified BED formula [Eq(C)] must be used 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.

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. Examples 1–5 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 6 elaborates on this and also discusses a treatment which does not begin on a Monday.

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

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. 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 6 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

After the gap, treatment resumes on the Monday of the seventh week of the schedule. Twenty-five fractions have been delivered and ten remain to be given. 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 6 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

In this example, the unscheduled gap extends to the time when treatment should have finished and any form of compensation will therefore 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.

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

$$35 \times 2 \times \left[1 + \frac{2}{3}\right] = 116.7 Gy_3$$

The BED_3 delivered before the gap is:

$$30 \times 2 \times \left[1 + \frac{2}{3}\right] = 100 Gy_3$$

The allowable BED_3 to left to give without increasing tolerance is therefore 116.7 – 100 = 16.7 Gy_3.

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

$$35 \times 2 \times \left[1 + \frac{2}{10}\right] - (46 - 28) \times 0.9 = 67.8 Gy_{10}$$

We begin by assuming that the missing dose is replaced by treating 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 $Gyday^{-1}$, the tumour BED^{10} will be lower than intended by an amount 7 × 0.9 = 6.3 Gy_{10}, ie 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 BED_{10} will be low by an even smaller amount of 3 × 0.9 = 2.7 Gy_{10} (4%). In each of these instances, the normal tissue BED_3 will again be as prescribed.

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 fractions, 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 BED_{10} of 67.8 Gy_{10} is to be maintained. Therefore, for the whole schedule (pre-gap plus post-gap):

BED_{10} (pre-gap) + BED_{10} (post-gap) – tumour repopulation factor = prescribed BED_{10}

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

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.

For the normal tissue, the compensated treatment increases the BED_3 to:

BED_3 (pre-gap) + BED_3 (post-gap)

ie:

$$100 + 5 \times 2.62 \times \left[1 + \frac{2.62}{3}\right] = 124.5 Gy_3$$

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):

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

That is, 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', ie 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:

BED_{10} (pre-gap) + BED_{10} (post-gap) – tumour repopulation factor

ie:

$$30 \times 2 \times \left[1 + \frac{2}{10} \right] + 5 \times 2.3 \times \left[1 + \frac{2.3}{10} \right] - (51 - 28) \times 0.9 = 65.4 Gy_{10}$$

The normal tissue BED is:

BED_3 (pre-gap) + BED_3 (post-gap)

ie:

$$30 \times 2 \times \left[1 + \frac{2}{3} \right] + 5 \times 2.3 \times \left[1 + \frac{2.3}{3} \right] = 120.3 Gy_3$$

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 examples for more complex cases

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 examples highlight 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

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.

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:

BED_3 (pre-gap) + BED_3 (post-gap) = Required BED_3

ie:

for which d = 3.22 Gy

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

BED_{10} (pre-gap) + BED_{10} (post-gap) – tumour repopulation factor

ie:

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

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 BED_{10} then being 61.9 Gy_{10}. This latter value is still 8.7% short of the prescribed tumour BED_{10} (67.8 Gy_{10}), 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 – extend 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:

BED_{10} (pre-gap) + BED_{10} (post-gap) – tumour repopulation factor

ie:

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

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.

Example 5. Loss of the final 13 fractions of a treatment schedule of 70 Gy/35 fractions/46 days

This represents a very difficult case. As a compromise between minimising the extension while at the same time ensuring that a reasonable number of fractions are used, we assume that ten post-gap fractions will be given, twice daily from Saturday to Wednesday, extending the treatment to 46 + 5 = 51 days. We first assume that the effect of incomplete repair is negligible, ie that Eq(A) remains valid. The relevant equation to determine the dose per fraction (d) to maintain the prescribed normal tissue BED_3 (116.7 Gy_3) is:

BED_3 (pre-gap) + BED_3 (post-gap) = Required BED_3

ie:

$$22 \times 2 \times \left[1 + \frac{2}{3}\right] + 10 \times d \times \left[1 + \frac{d}{3}\right] = 116.7 Gy_3$$

For which d = 2.41 Gy. The resultant tumour BED_{10} would then be:

BED_{10} (pre-gap) + BED_{10} (post-gap) – tumour repopulation factor

ie:

$$22 \times 2 \times \left[1 + \frac{2}{10}\right] + 10 \times 2.41 \times \left[1 + \frac{2.41}{10}\right] - (51 - 28) \times 0.9 = 62.0 Gy_{10}$$

To allow for the possibility of incomplete repair in the critical normal tissue Eq(C) is used for calculating the post-gap BED_3. Eq(C) requires prior evaluation [using Eq(D)) or (E) of the h factor, which in turn requires an assumption to be made about the nature of the repair kinetics. Mono-exponential repair half-times for late-normal tissues are often assumed to be of the order of 1.5 hours, but there is evidence that they may be longer for head and neck morbidity. Bentzen *et al*[110] investigated the repair half-times of three normal tissue endpoints from an analysis of the CHART head and neck data and found these to be in the range 3.8–4.9h. Taking a mid-range value of 4.5h, this corresponds to an exponential repair rate (μ) of $0.15h^{-1}$. (The repair rate is related to repair half-time via: μ = 0.693/half-time). If the post-gap daily fractions are 6h apart and that there is an 18-hour overnight gap, it is easier to calculate h only for the shorter time interval between any two adjacent fractions. This is because the incomplete repair after the longer (18-hour) gaps is *relatively* negligible compared with that following each 6-hour gap. Using Eq(D) with N = 2, x = 6 hours and $\mu = 0.15h^{-1}$, h is calculated to be 0.407. The normal tissue BED_3 then becomes, from Eqs(A) and (C):

BED_3 (pre-gap) + BED_3 (post-gap)

ie:

$$22 \times 2 \times \left[1 + \frac{2}{3}\right] + 10 \times 2.41 \times \left[1 + \frac{2.41 \times (1 + 0.407)}{3}\right] = 124.7 Gy_3$$

This is 6.7% higher than the value calculated when incomplete repair is ignored. If the twice-daily fractions were to be spaced at four-hour intervals then the h factor is 0.549 and BED_3 increases further to 127.4 Gy_3; that is, 9.1% higher than when incomplete repair is ignored. (Because the h factors are based only on the shorter inter-fraction intervals the consequent BED_3 values are slightly underestimated as there will be an additional amount of incomplete repair following the longer, overnight intervals. This 'overnight' contribution will become more significant as the number of successive days on which multiple treatments is delivered is increased.)

It has been speculated[111] that the sub-lethal damage repair may not be exponential in form (as conventionally assumed) but may proceed at a slower rate than is predicted by a single exponential function. A new 'reciprocal time' model of repair, built on this supposition, has been found to give an excellent fit a to a wide range of experimental repair data and, unlike models based on the mono-exponential repair mechanism, helps explain the cases of radiation myelopathy observed in the CHART trial. The h factors in the reciprocal time model may be calculated from Eq(E) in the Appendix and used directly in Eq(C).

Example 6. A nominal four-week head and neck schedule beginning on a Wednesday is prescribed as 54 Gy/20 fractions/27 days. The patient is too unwell to be treated for the last seven scheduled fractions and their deferment extends eventual completion of treatment to 38 days.

This treatment began on a Wednesday and the expected treatment time (with no treatment at weekends) is 27 days, rather than 25 days if it had began on a Monday.

The prescribed normal tissue BED_3 is:

$$54 \times \left[1 + \frac{2.7}{3} \right] = 102.6 Gy_3$$

Because the overall time is extended from 27 to 38 days we assume for calculation purposes that K is zero in the time up to 28 days and 0.9 $Gyday^{-1}$ thereafter. The prescribed tumour BED is therefore:

$$54 \times \left[1 + \frac{2.7}{10} \right] = 68.6 Gy_{10}$$

The interruption extends the overall time to 38 days. If the seven outstanding fractions were treated at the original fraction size (2.8 Gy) the late-reaction normal tissue BED_3 would be unaltered. However, the tumour BED_{10} will be compromised because the treatment has extended beyond the 28 days at which time faster tumour repopulation is assumed to begin. The tumour BED_{10} would then be calculated from:

BED_{10} (pre-gap) + BED_{10} (post-gap) – tumour repopulation factor

ie:

$$13 \times 2.7 \times \left[1 + \frac{2.7}{10} \right] + 7 \times 2.7 \times \left[1 + \frac{2.7}{10} \right] - (38 - 28) \times 0.9 = 59.6 Gy_{10}$$

a reduction of 13.1%.

In short-duration treatments of this type, the dose per fraction is already relatively large and any further increase (as may be required to strike a balance between normal tissue and tumour BEDs) should be considered with caution. As an example, to achieve a tumour BED_{10} with an intermediate value 65.0 Gy_{10} requires a dose per fraction (d) which is obtained from:

BED_{10} (pre-gap) + BED_{10} (post-gap) – tumour repopulation factor = required BED_{10}

ie:

$$13 \times 2.7 \times \left[1 + \frac{2.7}{10} \right] + 7 \times d \times \left[1 + \frac{d}{10} \right] - (38 - 28) \times 0.9 = 65.0 Gy_{10}$$

ie: d = 3.19 Gy per fraction.

Use of this fraction size for the deferred seven treatments would increase the normal tissue BED_3 to:

BED_3 (pre-gap) + BED_3 (post-gap)

ie:

$$13 \times 2.7 \times \left[1 + \frac{2.7}{3} \right] + 7 \times 3.19 \times \left[1 + \frac{3.19}{3} \right] = 112.8 Gy_3$$

This is still 10% more than that prescribed, even though the tumour BED_{10} has been deliberately compromised.

A final difficulty with interrupted schedules which already employ large fraction sizes is that the scope for post-gap acceleration using twice-daily treatments is limited on account of the large total daily doses which would result. In this particular example, bi-daily fractionation would deliver a total daily dose of 2 × 2.7 Gy, corresponding to a BED_3 delivery rate of 10.3 Gy_3 per day. This is over 50% higher than the BED_3 delivery rate (6.8 Gy_3 per day) associated with the thrice-daily fractionation of CHART, which itself is very similar to 2 × 2 Gy daily fractionation (6.7 Gy_3 per day).

These figures take no account of incomplete repair, which would increase the BED_3 associated with 2 × 2.7 Gy further. Even with well-spaced fractions, some caution would be required when contemplating daily biological doses of this magnitude and the possibility of treating bi-daily with a significantly reduced fractional dose should be explored.

Equations

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

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

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.

Calculation of tumour BED:

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

where T is the overall treatment time and T_{delay} the time lag (from beginning of treatment) before rapid tumour repopulation begins to occur. K is the daily BED-equivalent (units $Gyday^{-1}$) of repopulation.

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

$$BED = Nd \times \left[1 + \frac{d(1+h)}{\alpha/\beta} \right] .... Eq(C)$$

where h is calculated from Eq(D) (for mono-exponential repair kinetics) or Eq(E) (for reciprocal-time repair kinetics).

$$h \times \left(\frac{2}{n}\right) \cdot \left[\frac{\theta}{(1-\theta)}\right] \cdot \left[\frac{(1-\theta^n)}{(1-\theta)}\right] .... Eq(D)$$

In Eq(D) n is the number of fractions in a 'group' of closely spaced fractions and θ = exp(-μx), where μ is the exponential repair constant of sub-lethal damage and x is the average time interval (h) between these closely-spaced fractions. For late-responding normal tissues μ is often assumed to have a generic value of $0.5h^{-1}$; for prediction of radiation myelopathy subsequent to head and neck radiotherapy a smaller value of around $0.22h^{-1}$ was found to be more appropriate.[1]

$$h \times \left(\frac{2}{n}\right) \sum_{i=2}^{n} \frac{(n+1-i)}{[1+zx\,(i-1)]} .... Eq(E)$$

In this model, Eq(E) z is the reciprocal-time repair constant of sub-lethal damage. For example, the myelopathies observed in the CHART Trial are consistent with a z value for spinal cord of $0.36h^{-1}$.[112]

Provided there are only a few consecutive days on which multiple daily fractions are delivered the calculation of h using either Eq(D) or Eq(E) may be simplified by taking into account only the shortest inter-fraction intervals. For example, if twice-daily fractionation is being used with an interval of 6h between fractions, followed by an longer overnight interval of 18h, the values used to calculate h are N = 2 and x = 6. Allowance for the additional incomplete repair following the longer overnight intervals may become necessary if there are many successive days on which twice-daily fractions is delivered. Buckle and Lewis[113] provides more details on this.

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 very 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 is probably necessary.
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, vulva, breast, head and neck) 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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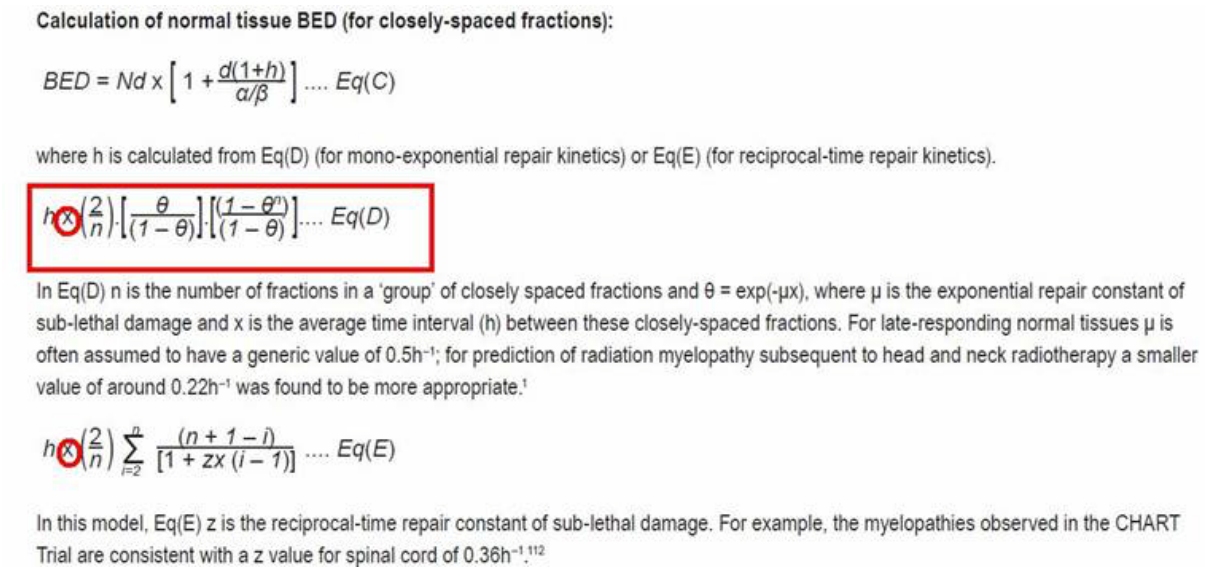
Erratum

***The timely delivery of radical radiotherapy: standards and guidelines for the management of unscheduled treatment interruptions*, Third edition, 2008**

Please note on page 29 of the above document, the equations D and E are incorrect.

The circles show where a multiplication sign has been inserted in Equations (D) and (E) where it should have been an **equals (=)** sign.



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

$$BED = Nd \times \left[1 + \frac{d(1+h)}{\alpha/\beta}\right] \ldots. Eq(C)$$

where h is calculated from Eq(D) (for mono-exponential repair kinetics) or Eq(E) (for reciprocal-time repair kinetics).

$$h \otimes \left(\frac{2}{n}\right).\left[\frac{\theta}{(1-\theta)}\right].\left[\frac{(1-\theta^n)}{(1-\theta)}\right] \ldots. Eq(D)$$

In Eq(D) n is the number of fractions in a 'group' of closely spaced fractions and θ = exp(-μx), where μ is the exponential repair constant of sub-lethal damage and x is the average time interval (h) between these closely-spaced fractions. For late-responding normal tissues μ is often assumed to have a generic value of $0.5h^{-1}$; for prediction of radiation myelopathy subsequent to head and neck radiotherapy a smaller value of around $0.22h^{-1}$ was found to be more appropriate.[1]

$$h \otimes \left(\frac{2}{n}\right) \sum_{i=2}^{n} \frac{(n+1-i)}{[1+zx\,(i-1)]} \ldots. Eq(E)$$

In this model, Eq(E) z is the reciprocal-time repair constant of sub-lethal damage. For example, the myelopathies observed in the CHART Trial are consistent with a z value for spinal cord of $0.36h^{-1}$.[1,12]

The red box shows equation (D) which is different from the published versions in Thames 1985 and in reference 29 (Basic Clinical Radiobiology by Steel) and from any of the associated Dale publications.

It should be

$$h = \left(\frac{2}{n}\right).\left[\frac{\theta}{(1-\theta)}\right].\left[n - \frac{(1-\theta^n)}{(1-\theta)}\right] \ldots. Eq(D)$$