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Radiotherapy treatment interruptions during the Covid-19 pandemic: The UK experience and implications for radiobiology training

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ABSTRACT

Unintended treatment interruptions during a course of radiotherapy can lead to extended overall treatment times which allow increased tumour cell repopulation to occur. Extra dose may therefore be required to offset any loss of tumour control. However, the manner in which the extra dose is delivered requires careful consideration in order to avoid the risk of increased normal tissue toxicity. Radiobiological modelling techniques can allow quantitative examination of such problems and may be used to derive revised pattens of radiation delivery which can help restore a degree of tumour control whilst limiting the likelihood of excess normal tissue morbidity. Unintended treatment interruptions can occur in any radiotherapy department but the rapid spread of the Covid-19 pandemic caused a major increase in the frequency of such interruptions due to staff and patient illness and the consequent self-isolation requirements. This article summarises the radiobiological considerations and caveats involved in assessing treatment interruptions and outlines the UK experience of dealing with the new challenges posed by Covid-19. The world-wide need for more education programmes in cancer radiobiology is highlighted.

1. Introduction

For many fast-growing cancers there is a wealth of clinical evidence which demonstrates that uncompensated interruptions to radiotherapy, resulting in prolongation of the overall treatment time, increases the risk of local recurrence of such tumours (e.g. Barton et al., 1992, Royal College of Radiologists, 2019). This observation applies to all type of radiotherapy, i.e. radical primary treatments, radical post-operative treatments, chemoradiotherapy and treatments which combine external beam radiotherapy with brachytherapy. For some tumor types (e.g. squamous cell cancers, cervix cancers, lung cancers) extensions to treatment time can lead to a notional loss in tumour control of between 0.8 and 1.6% for each day of treatment extension (Fowler and Lindstrom, 1992; Petereit et al., 1995). An uncorrected treatment extension of seven days could therefore be associated with loss in tumour control of up to 10%. In cases involving particularly aggressive tumours, treatment extensions of just two days have been reported to cause a clinically detectable loss of local tumour control (Bese et al., 2007).

It should be noted that treatment gaps per se are not the main issue here; the problem stems from any consequent extension to the overall treatment duration beyond that originally prescribed. Avoidance of treatment interruptions is therefore a matter of some importance, as is an understanding of what compensatory measures are available to help reclaim some of the lost tumour control when unscheduled treatment extensions do occur. In the UK the Royal College of Radiologists (RCR) has published extensive national guidelines and the degree of prioritisation to be assigned to patients whose treatments have been interrupted is broken down into three categories (Royal College of Radiologists, 2019):

Category 1. Patients with fast-growing tumours which are being treated radically and for which there is strong evidence that treatment prolongation have a detectable detrimental effect.
Category 2. Patients with slower-growing tumours being treated radically and for which there is evidence that treatment prolongation of more than five days have a detrimental effect on local control and survival.
Category 3. Patients being treated palliatively and for whom overall time considerations are less critical. However, long treatment extensions (e.g. of more than seven days) may require compensatory measures.

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The full list of tumour types falling within each of the above categories is given in the RCR guidelines. For patients in Categories 1 and 2 in particular every attempt should be made to adhere to the overall treatment time inherently specified within their treatment prescription. This may involve arranging in advance to treat during Public Holidays when such days occur during a schedule, a measure which has obvious financial implications.

When interruptions do occur attempts should first be made to avoid there being a consequent extension to the overall treatment time. The steps to be considered may be summarised as follows:

- If unscheduled interruptions result from a technical failure then, where feasible, patients should be transferred to a second machine to ensure treatment continuity.
  Relatively short interruptions, and those occurring early in the schedule, may often be compensated for by treating some of the remaining treatment fractions twice-daily and/or at weekends. Bi-daily fractionation requires that the fractions should be spaced at least 6 h apart and, if several such treatment days are necessary, these should ideally be interspersed with "normal" single fraction treatment days. Alternatively, and where feasible, the bi-daily treatments could be arranged at the end of the working week, thus allowing a weekend break before resuming with the normal scheduling. Such steps are necessary to limit the risk of incomplete repair occurring in the normal tissues. Provided these conditions can be met then overall times may be exactly (or closely) maintained and there need be no alteration to the originally-prescribed fractional dose.
  Where simple treatment restoration measures are not possible (i.e. when treatment extensions are inevitable) then it may be necessary to increase the treatment dose in order to avoid excessive loss of tumour control and radiobiologically-based calculations may be required.

The likelihood of being able to make a successful treatment compensation is primarily dependent on three factors, as shown in Table 1.

2. Outline of relevant radiobiology

At the beginning of a radiotherapy treatment many tumour cells will be well-distanced from the blood capillaries and will therefore be in varying states of hypoxia. They will be either quiescent or multiplying at a much slower rate than when they were first created. Additionally, at the start of a treatment, the cell loss factor (CLF) is normally high, especially in large volume tumours. As radiotherapy progresses the tumour diminishes in size, vascularity starts to improve and the CLF falls. As a consequence, any cells which have not already been sterilised by the radiation start to become better oxygenated and begin to grow (repopulate) at, or close to, their fastest rate, characterised by the potential doubling time, T_{pot}. For the more aggressive tumours T_{pot} values may be surprisingly low, frequently much less than seven days and corresponding to fast rates of repopulation (Begg et al., 1990; Hausterman et al., 1997; Rew and Wilson, 2000). Paradoxically, therefore, any tumour cells which remain extant near the end of a treatment may be growing at their fastest rate. If a treatment is extended at this point then the added time will allow for the birth of yet more cells and, unless extra dose is added, eradication of the newly-created cells becomes less likely and tumour control is compromised.

The kinetics of tumour repopulation is summarised pictorially in Fig. 1, which illustrates how the total dose required to maintain a given degree of tumour control varies with the overall time taken to deliver the treatment (Withers et al., 1988). The characteristic "dog-leg" shape of the graph shows that there is a delay time of a few weeks from the initiation of treatment before fast repopulation starts to occur and then it proceeds at a fairly constant rate. Uncompensated interruptions which cause treatment times to extend into this period are therefore especially problematic.

Table 1
Qualitative links between gap duration, gap position and tumour type on difficulty of compensation.

	Less difficult cases	More difficult cases
Duration of gap	Short	Long
Position of gap	Early in schedule	Late in schedule
Tumour type	Slow-growing	Fast-growing

3. Radiobiological calculations

The calculation processes required for devising treatment compensations are derived from the well-known linear-quadratic (LQ) dose-response model and utilise the derived concept of biologically effective dose (BED). The essential elements have been discussed in depth elsewhere (Dale, 1985, 1989; Jones et al., 2001; Fowler, 2010; Jones and Dale, 2019) and only a brief summary is given here.

BED is the primary measure of radiation effect and, in conventional fractionated external-beam radiotherapy (where the dose fractions are 24h or more apart) takes account of the type of tissue irradiated, total dose, number of fractions (and hence, the dose per fraction) and overall treatment time. More advanced formulations for BED can take account of closely-spaced fractions (Dale, 1986) but are not considered here.

The primary radiobiological parameters required for the calculations are:

Tissue-specific α/β values. These are the ratios between the linear and quadratic radiosensitivity coefficients which characterise the LQ model. α/β is an inverse measure of the fractionation sensitivity of a given tissue or organ. Late-responding normal tissues (which usually set the limit on how much dose may be delivered in a radiotherapy schedule) are generally more fractionation sensitive than tumours and, as such, usually possess lower α/β values than tumours.
K-factors. The K factor (in units of Gyday^{-1}) is the BED-equivalent of the daily dose required to sterilise the new cells created following commencement of significant repopulation, i.e. K is related to the rising slope in Fig(1).
The delay factor, T_{delay}. As illustrated in Fig(1), T_{delay} is the lag time from the initiation of treatment before fast repopulation begins.

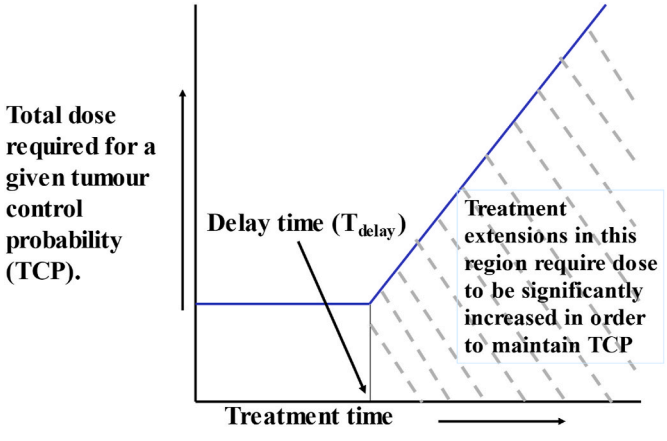

Fig. 1. Pictorial demonstration of how the dose required to maintain a given TCP depends on the overall treatment time. Tumour repopulation remains close to zero following initiation of treatment, meaning that the dose required to maintain TCP is largely unvarying (horizontal line). After a delay of a few weeks the remaining cells begin to repopulate at a fast rate and the extra dose required to sterilise the new cell and maintain TCP rises linearly with increasing time. (Withers et al., 1988).

Some standard parameters are published (e.g. Wigg, 2001; Bentzen and Joiner, 2019) but supplementary suggestions were made during the Covid-19 pandemic (Jones et al., 2021).

The dose-prescription factors included in BED calculations are dose per fraction (d), number of fractions (N) and overall treatment time (T). For most compensation assessments two BED values are required, BED_{tum} and BED_{late}:

For tumours:

$$BED_{tum} = Nd\left[1 + \frac{d}{(\alpha/\beta)_{tum}}\right] - K(T - Tdelay) \quad (1)$$

where $(\alpha/\beta)_{tum}$ usually takes a generic value of 10Gy. Notable exceptions are breast cancer and some types of prostate cancer which possess lower α/β values, respectively around 4Gy and 1.5Gy.

For late-responding normal tissues (for which cellular repopulation during treatment is zero):

$$BED_{late} = Nd\left[1 + \frac{d}{(\alpha/\beta)_{late}}\right] \quad (2)$$

where $(\alpha/\beta)_{late}$ takes a generic value of 3Gy. The exception is spinal cord, which takes a value of 2Gy.

Appropriate values of d, N and T are used in Eqs (1) and (2) to calculate the prescribed normal tissue and tumour BEDs (respectively denoted A and B), along with the BEDs delivered at the time the interruption began (respectively denoted C and D). From these four numbers may be derived the remaining BEDs required to restore the precription values once treatment re-starts, in the manner shown below.

	Prescribed BEDs	BEDs to gap	BEDs required to restore prescription values after treatment re-starts.
Tumour	A	C	(A – C)
Normal tissue	B	D	(B - D)

It should be noted that the quantity (A – C) is the minimum BED ideally required for the tumour, whereas the quantity (B - D) would normally be considered the maximum remaining BED allowable for the normal tissue. Once these "ideal" values have been computed, the following steps are required in order to determine a viable compensation scheme:

- Decide on the compensation approach to adopt, e.g. a few fractions with increased dose/fraction, larger number of bi-daily fractions with smaller dose/fraction, etc. Using Eq (2) first determine the number of fractions and/or dose/fraction which will ensure that the originally-prescribed normal tissue BED is not exceeded.
- Use this revised fractionation scheme to calculate the total tumour BED which will be delivered by the entire (pre-gap + post-gap) treatment and compare this with the prescribed tumour BED. Determine if any of the proposed compensation schemes restore the tumour BED close to that required. If so then a reasonably good compensation has been found.
- If tumour BED cannot be closely or fully restored to that originally prescribed (as is frequently the case when long interruptions are involved) then a compromise between reduced tumour BED and slightly increased normal tissue BED may be necessary. This is a decision which will need to take account of specific patient–related factors (age, prognosis, concomitant health conditions, risk factors, etc) and input from the responsible clinician is essential at this stage. Then examine the possibilities (e.g. small increases in dose/fraction in the post-gap schedule, bi-daily fractionation, etc) which will provide a reasonable trade-off between an increased normal tissue BED and a reduced tumour BED. It should be noted that, although bi-daily fractionation is a viable option when considering interruptions to conventional fractionation schemes, it cannot be considered for hypofractionated treatments which already employ large fractional doses.

A more-in-depth discussion of these considerations and procedures is available elsewhere (e.g. Dale et al., 2002; Royal College of Radiologists, 2019). These publications also discuss the more complex formulations which may sometimes be required when bi-daily fractionation has to be employed over several successive days.

4. The impact of Covid-19

The need for patients to self-isolate and/or the non-availability of key treatment staff during the pandemic has caused unscheduled interruption of many treatments. In a few instances the interruptions were of very long duration (i.e.months) and to an extent where, particularly when spinal cord was involved, re-commencement of radiotherapy could be regarded as a new treatment (Woolley et al., 2018). In other cases, and for certain treatment sites, the pandemic has helped accelerate the switch from traditional schedules (occupying several weeks) to much shorter schedules. In the particular case of breast cancer there is sound clinical evidence that a short schedule of five fractions delivered in one week is at least as effective as the traditional longer schedules (Brunt et al., 2020), although the choice of dose is important to minimise late normal tissue effects. Such reductions in overall treatment time lessen the likelihood of interruptions occurring and also allow an increase in machine treatment capacity. The possibility of using such wholesale schedule changes is, however, limited to only a few tumour sites.

In the UK the pandemic brought with it an increased awareness of the problems which treatment interruptions present. An earlier (pre-Covid) survey (Dale et al., 2007) confirmed that many Centres possess some degree of in-house expertise for dealing with routine radiobiological calculations but, even at that time, a frequent comment made by the survey responders was that there should be more formalised training in the radiobiological aspects of treatment interruptions. The arrival of Covid-19 created particular problems associated with long or multiply-interrupted treatments, along with concerns over which parameter values to use, and this resulted in the establishment of a small group of expert volunteers, any of whom could be contacted if assistance was required with individual cases. At the same time further practical advice was made available via the Royal College of Radiologists website and the availability of this information helped restrict the number of queries directed to the expert volunteers. However, and as with the 2007 survey, it was again clear from the more general feedback that many clinicians and medical physicists would welcome a more formalised education on several aspects of radiobiology and how this can best be achieved and maintained at a national level remains the subject of ongoing discussion. Interestingly, several requests for advice were received from Centres outside the UK, suggesting that radiobiology educational concerns may be a more general issue.

Predictably, the pandemic once again prompted questions relating to the appropriate radiobiological parameter values to use when performing compensation calculations. This has long been a difficult area since reliable human clinical data are available for only a few tumour sites. An additional complication is that the necessary parameters are not merely specific to the tumour histology, they can also vary according to tumour grade, meaning that the choice of parameters may need to be refined in some instances. For example, if a tumour is histologically designated as poorly differentiated or anaplastic, it may be reasonable to modify both the α/β ratio and the repopulation factor to higher values. Thus, for a breast or prostate cancer with such histological features, better α/β and K values to assume would be 10Gy and 0.6 $Gyday^{-1}$ respectively.

There will also be occasions when one of the parameters is not well known. In such cases, a reciprocal relationship of $\alpha/\beta = 48.8/T_{pot}$ may be employed (Jones, 2017). If it is also assumed that T_{pot} values are

between 2 and 4 days (mean of 3 days) for squamous cell cancers during accelerated repopulation (when the K factor approaches a high value of around 1Gy per day) then a further useful reciprocal relationship would be $K = 3/T_{pot}$. This would indicate K values of 0.3, 0.2 and 0.15 Gy/day for T_{pot} values of 10, 15 and 20 days respectively, this covering the approximate range seen in prostate and breast cancers. For medulloblastoma, where $\alpha/\beta = 28$Gy, the estimated T_{pot} is $48.8/28 = 1.7$ days which, if rounded to 2 days, leads to an estimated K value of $3/2 = 1.5$ Gyday^{-1}. Such adjustments can be regarded as reasonable in situations where parameters are not well established, but further research in this area is required.

With the above issues in mind an updated range of parameter suggestions were made during the pandemic and circulated to all UK radiotherapy and radiotherapy physics departments via the Royal College of Radiologists and the Institute of Physics and Engineering in Medicine, (Jones et al., 2021), the proviso being that radiobiological parameters are continually refined and need to be kept under constant review.

5. Discussion

The increased awareness of the relevance of treatment gap compensation has also highlighted the importance of establishing an appropriate level of radiobiological understanding amongst radiotherapy healthcare professionals (Jones and Dale, 2020).

In reality, there are many aspects of modern radiotherapy which would benefit from improved radiobiological appreciation and the issue of gap compensation is but one of them. Advancements in technology (e.g. proton and ion therapy, biologically-vectored radiotherapy, stereotactic ablative body radiotherapy, etc) have introduced a number of potentially exciting improvements to radiotherapy practice, but such developments often enter routine use before the associated radiobiological aspects are fully evaluated.

World-wide, around 1 in 5 people can expect to develop cancer in their lifetimes but in developed nations the figure is closer to 1 in 2. Improved longevity and altered life-styles are the prime drivers of an ever-increasing cancer incidence and overall case numbers are expected to double by 2040 (WHO/IARC, 2020). Such statistics will ensure that radiotherapy, already established as a primary and successful treatment modality, will face more demands than ever over the coming decades and from this it follows that radiobiology education will need to grow in parallel.

The current UK training position in cancer radiobiology is somewhat variable. Junior clinical oncologists follow the subject as far as their Part 1 examinations with little further coverage in Part 2, although specialised (non-mandatory) masters-level courses do provide a more in-depth coverage. For medical physicists some radiobiology is included within the basic training programme which all have to pursue in order to be eligible to join the UK state register. The depth of coverage of underlying principles is somewhat limited but an option to study radiobiology to an advanced level is now incorporated within the UK Higher Specialist Scientist Training Programme. The syllabus at that level is significantly more comprehensive (https://curriculumlibrary.nshcs.org.uk/hsst/module/HPE124/) and presents a valuable training opportunity. However, there is currently no requirement to make attendance compulsory for all radiotherapy physicists. The major international radiotherapeutic organisations (e.g. ASTRO, ESTRO, FAORO, etc) also provide short courses on various aspects of radiobiology but, again, registration for attending these is essentially voluntary.

6. Conclusion

An understanding of radiobiology (including quantitative modelling aspects) is essential to the successful pursuit of radiotherapy. Radiation oncologists, medical physicists, technologists etc, should all undergo a grounding in the subject at a depth appropriate to their respective professional expectations. The methods used to assess radiobiological understanding also need to be reviewed since training of the sort that requires only MCQ or "tick-box" assessments of competence is arguably inadequate for specialist practitioners. At present the UK educational requirements, although improving in some areas, remain somewhat short of ideal and this likely reflects a more general world-wide problem. In some cases it may be appropriate to designate national experts who can provide radiobiology advice but this should not detract from the more pressing requirement for more focussed training of a new generation of practioners. Aside from any Covid-related considerations this will also be necessary to ensure that the radiobiological aspects are always considered when determining the best use of emerging radiotherapy technologies. The challenges introduced by the Covid-19 pandemic have brought such issues into sharper focus and there is now an urgent need for professional bodies to consider how best to respond.

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R.G. Dale: Conceptualization , Investigation. **B. Jones:** Conceptualization, Data curation, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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