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Correction

# Corrigendum: Estimation of the effects of radiotherapy treatment delays on tumour responses: A review

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This correction does not alter the study's findings of significance or overall interpretation of the study's results. The authors apologise for any inconvenience caused.

# Estimation of the effects of radiotherapy treatment delays on tumour responses: A review



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Scan this QR code with your smart phone or mobile device to read online. **Background:** The effects of radiotherapy treatment delays vary considerably depending on several factors, including tumour type, tumour characteristics, extent of delay and the radiation schedule. Both delays during treatment and delays in starting treatment may have an impact on tumour outcomes. In developing countries, particularly, budget constraints and overwhelming patient numbers may contribute to long waiting lists that may affect treatment efficacy. Empirical evidence on which to base treatment decisions and to motivate for additional resources is important.

**Aim:** The aim of this study was to review the evidence that radiotherapy treatment delays may affect tumour response in several common tumour types and to determine, where reported, estimates of specific, commonly applied parameters to incorporate time and proliferation.

Setting: Clinical radiotherapy of solid tumours.

**Methods:** A review of the literature from an online database and search engine using terms associated with treatment delays or interruptions for a range of common tumour types was conducted.

**Results:** There is evidence in several of the tumour types reviewed, including those of the head and neck, breast, cervix, prostate, lung, colorectal, anus, brain and bladder, that delays in radiotherapy can affect treatment outcomes. While, in most cases, delays in treatment are detrimental, there are certain examples cited where delays between other modalities and radiotherapy may be beneficial.

**Conclusion:** While levels of evidence vary, failure to take note of proliferative effects of tumours because of extensions in treatment may in many cases result in avoidable treatment failures. It is thus prudent for radiation oncology departments to have clear policies for avoiding and dealing with treatment delays.

**Keywords:** tumour repopulation; radiotherapy; treatment gaps; proliferation; overall treatment time.

# Introduction

Many developing countries like South Africa are faced with limited resources and long radiotherapy waiting lists. Extensions in overall radiotherapy treatment times may be detrimental to patient outcomes because of accelerated tumour cell proliferation. Accelerated repopulation, that is, an increase in the rate of tumour cell division after a certain time into radiotherapy, may result from a decrease in tumour cell loss and an increase in tumour cell recruitment into the mitotic cycle, which occur when increased oxygen and nutrients become available when tumour cells are sterilised by irradiation.<sup>12</sup> Accelerated repopulation may also be a result of radiation-induced activation of cell proliferation signalling.<sup>3</sup>

It is generally accepted that radiotherapy should ideally be completed without significant delays so as not to adversely affect tumour control or patient survival. However, given the extended nature of fractionated radiotherapy, which typically takes several weeks, it is common for treatments to be delayed for a variety of medical, logistic and social reasons. Delays in the initiation of treatment may also be detrimental to patient outcomes. The impact of alterations in overall treatment time or time till treatment may vary depending on tumour type, tumour stage, tumour biology, use of other anticancer treatments and whether any radiobiological compensation may have been applied to mitigate such alterations. While the primary focus of this review is on delays in radiotherapy, the issue of accelerated repopulation and effect of delays may also be relevant to other cancer treatment modalities, including surgery and chemotherapy. Thus, the relevance of delays in all modalities and possibly the aggregate effects of all treatments need to be considered. Radiotherapy treatment interruptions are common. Planned gaps because of weekends or public holidays are often incorporated into treatment schedules up front and are generally easier to accommodate than unplanned gaps where there may be less flexibility for compensation. Preplanned modifications in scheduling can be spread over the treatment to reduce any impacts on the therapeutic ratio. Compensation for unplanned gaps may be more complicated, particularly if there have been multiple interruptions and limited available time in which to apply any compensation before the detrimental effects of treatment extension become significant.

There are pragmatic approaches for compensating for gaps in radiotherapy. If a treatment extension is negligible or a tumour is slowly proliferating, no compensation may be necessary. However, knowledge of specific tumour kinetics is often lacking, and it is best to prevent gaps if possible to keep treatments 'as short as reasonably achievable', as suggested by the guidelines of the Royal College of Radiologists.<sup>4</sup> If gaps have occurred, treatments should ideally be completed in the same overall time by treating on non-treatment days, delivering more than one fraction on a day or adding additional dose. If overall times are extended, compensation may also be possible by adding additional dose. The extra dose required would need to be determined using radiobiological dose equivalence estimates. The likelihood of normal tissue effects, whether tolerance is likely to be exceeded, and any effects on therapeutic ratio may also be estimated in this way. While treatment extensions are not considered good practice, there may be a case for extending treatments to keep fraction sizes small to maintain therapeutic advantage provided that the detriments of repopulation do not outweigh the advantages of normal tissue from fractionation.

Radiobiological effects may be estimated using an equation based on the linear-quadratic model:

 $EQD2 = nd(d+\alpha/\beta)/(2+\alpha/\beta),^{5}$  [Eqn 1]

where *n* is number of fractions, *d* is dose per fraction and  $\alpha/\beta$  is the fractionation dependence.

A modified version that includes time factors that may be relevant to tumour repopulation is:

$$EQD2 = nd(d + \alpha/\beta)/(2 + \alpha/\beta) - (T - Tk)Dprolif_{6}^{6}$$
 [Eqn 2]

where *T* is the overall treatment time, *Tk* is the time at which accelerated repopulation starts and *Dprolif* is the dose 'lost' per day because of proliferation. This equation takes into consideration the induction of more rapid tumour growth after the initiation of treatment and the associated reduction in tumour effect. The accuracy of any predictions, however, will depend on the assumptions used. In many cases, accurate values of *Tk* and *Dprolif* are not available. Nevertheless, there is considerable information available that may allow reasonable determinations of possible outcomes, depending upon likely best and worst cases.

Apart from accelerated repopulation, which may occur after initiation of therapy, significant proliferation prior to the initiation of therapy may also negatively affect therapeutic effectiveness. Departments, particularly those in lesser resourced or developing countries, may have long waiting lists and limited flexibility to compensate for extensive gaps. It may be better to delay the start of radiotherapy rather than introducing gaps into treatment so as to avoid the detrimental effects of accelerated repopulation. However, delays in starting treatment may also have a negative impact on treatment outcomes because of excessive tumour growth prior to treatment, resulting in increased treatment failure. Such variables should be incorporated into any cost–benefit analysis when allocating resources to oncology units.

To assess the likely impact of time on tumour outcomes and determine what compensation for treatment delays may be necessary, tumour-type-specific information is required. Moreover, to minimise the impact of delays, it is important to establish suitable biological parameters that may be used for specific clinical scenarios. Representative values of Tk and Dprolif, and the effect of delays in treatment for specific tumour types and schedules need to be determined, as well as the influence of more modern approaches such as hypofractionation or chemoradiotherapy.

We have undertaken a review of the evidence for accelerated repopulation in a variety of common tumours and how alterations in overall treatment time or time before the start of radiotherapy may influence treatment outcome.

# Methods

Medline and Google Scholar searches were used including terms such as 'gaps radiotherapy', 'interruptions radiotherapy', 'delays radiotherapy', 'breaks radiotherapy' and 'overall radiotherapy time' associated with various tumour sites.

In this review, evidence of the effects of treatment delays or extensions for head and neck, breast, cervix, prostate, lung, colorectal, brain and bladder cancers is presented besides estimates of certain relevant parameters pertaining to proliferative effects.

# Results and Discussion Head and neck tumours

There is substantial evidence of significant rates of repopulation for squamous cell carcinomas of the head and neck. Both extensions in overall treatment time and delays till start of radiotherapy are detrimental and should be avoided.

#### **Overall treatment time**

**Radiotherapy alone**: It has been estimated that for laryngeal cancer, an increased dose of 0.5–0.6 Gy per day is required to maintain local control, with a kick-off time of not more than

3 weeks after starting radiotherapy.<sup>7</sup> A study of more than 2200 laryngeal cancer patients showed that prolongation of therapy by 1 day was associated with a decreased 2-year control rate.<sup>8</sup> For nasopharyngeal cancer, the hazard rate for locoregional failure was found to increase by approximately 3.3% for each day of treatment interruption.<sup>9</sup>

**Chemoradiotherapy**: More recent studies that incorporate chemotherapy have shown that radiotherapy delays may adversely affect treatment outcomes. Prolonged radiotherapy resulted in inferior survival and an increased likelihood of locoregional recurrence even with induction chemotherapy and concurrent chemotherapy.<sup>10</sup> Treatments in excess of 7 weeks<sup>11</sup> and 8 weeks<sup>12</sup> were associated with inferior survival for patients receiving concurrent chemoradiotherapy. In another study, overall radiotherapy treatment times of more than 40 days significantly reduced metastasis-free survival by about 40% in patients with advanced disease treated with radiotherapy alone or with chemoradiotherapy.<sup>13</sup>

Time before treatment: Some studies suggested that increased waiting times between diagnosis and radiotherapy may not affect outcomes.<sup>14,15</sup> The majority of studies, however, demonstrated that delays in initiating radiotherapy resulted in inferior outcomes. A meta-analysis of quality studies published between 1975 and 2005 showed that for patients treated with definitive radiotherapy, there was an increase in the absolute risk of recurrence of about 3.7% per month of delay.16 A multivariate analysis of a prospective database of 9896 patients with nasopharyngeal carcinoma showed that waiting time before radical radiotherapy of greater than 30 days was associated with inferior overall survival and disease-specific survival.17 Longer waiting times till start of surgery have also been shown to adversely affect survival.<sup>18,19</sup> However, in a recent study, time between diagnosis and surgery did not influence survival.20

**Time between surgery and radiotherapy:** A meta-analysis found that, for patients treated with postoperative radiotherapy, the absolute risk of recurrence increased by about 6.3% for every month that radiotherapy was delayed.<sup>16</sup> An analysis of 15 064 patients showed that survival decreased progressively with each day that the start of radiotherapy was delayed beyond 40 days post-surgery up till 55 days, after which further prolongation failed to have any additional effect on survival.<sup>20</sup>

#### **Breast tumours**

#### **Overall treatment time**

Evidence regarding the effect of overall radiotherapy treatment time is sparse. One study suggested that patients at low risk of recurrence may be minimally affected by treatment delays.<sup>21</sup> However, another study of 853 patients with stage I–III breast cancer, all of whom had undergone surgery, and 84% of whom had received adjuvant chemo- or hormonal therapy, demonstrated a reduction in overall survival and

5-year local control for an extension in radiotherapy of more than 1 week.<sup>22</sup>

#### Time between surgery and radiotherapy

**Delays do not affect outcome**: Some studies showed little effect of waiting 6–8 weeks between surgery and radiotherapy for early, localised disease.<sup>23,24</sup>

**Delays improve outcome**: A comparison of three timing tertiles (1–36, 37–53 and 54–112 days) between lumpectomy and radiotherapy for patients with stage I or II, node-negative disease demonstrated that 10-year metastasis-free survival and disease-specific survival were superior for those who had a longer interval between treatments.<sup>25</sup>

**Delays worsen outcome**: A review of 46 studies found that recurrences were increased if time between surgery and radiotherapy exceeded 8 weeks.<sup>26</sup> Another systematic review suggested that 12 weeks was the cut-off.<sup>27</sup> A study of more than 18 000 patients showed that an interval of 6 weeks was significant with respect to loss of local control, with a hazard ratio of 1.19.<sup>28</sup> In a recent review, it was concluded that, to maintain acceptable outcomes (< 3% – 4% loss of survival), time between surgery and radiotherapy should not exceed 20 weeks.<sup>29</sup> Other recommendations were that surgery should occur within 90 days of diagnosis, chemotherapy within 120 days of diagnosis and radiotherapy within 365 days of chemotherapy.

#### **Cervical tumours**

**Overall treatment time**: There is substantial evidence that tumour cell repopulation occurs as a result of extensions in the overall radiotherapy treatment time and negatively affects outcomes. A loss of overall survival and local control of 0.6% per day, irrespective of tumour grade,<sup>30</sup> and 1% per day for advanced disease<sup>31</sup> was reported for extensions beyond 52–55 days. An earlier study suggested that, for patients with advanced disease, extensions beyond 30 days may adversely affect outcome.<sup>32</sup> In a 2004 study, overall survival, disease-free survival and local control were found to be superior for treatment times of 60 days or less.<sup>33</sup>

Combination chemoradiotherapy may influence the effects of treatment extensions. A retrospective review of 113 patients with stage IB2-IIIB disease, who received whole pelvis chemotherapy radiotherapy with concurrent and brachytherapy to the cervix, confirmed the importance of completing the brachytherapy within 8 weeks to avoid pelvic failure.<sup>34</sup> A study of 2594 patients, the majority of whom were treated with chemoradiotherapy, showed that for early-stage patients (I-IIB), survival was worse when treatment times were longer than 56 days. However, for advanced disease (III-IVA), no effect on outcomes could be demonstrated.<sup>35</sup> A small retrospective study of 166 patients receiving chemoradiotherapy and 206 patients receiving radiotherapy

found a trend for treatment durations of 62 or more days to result in a worse disease-free survival, but only in women treated with radiotherapy alone.<sup>36</sup> A large study of 7209 patients receiving chemoradiotherapy could not demonstrate a difference in the overall survival in patients treated in 8 weeks or less versus those treated in more than 8 weeks. Survival, however, was found to be inferior when the treatment duration exceeded 10 weeks.<sup>37</sup> It is possible that chemotherapy combined with radiotherapy may, to some extent, inhibit radiation-induced accelerated repopulation.

#### Tk and Dprolif

From clinical data, a Tk value of around 19 days was estimated.<sup>38</sup>

For an assumed *Tk* of 28 days, *Dprolif* values of 0.22–0.31 Gy/day for relatively radiosensitive tumours and 0.5 Gy/day for radioresistant tumours were estimated.<sup>33</sup>

#### Time before treatment

Delaying the start of radical radiotherapy may adversely affect outcome.<sup>39</sup> A large study comprising 9081 patients showed that delaying surgery, radiotherapy or chemoradiotherapy by 4 or more months after diagnosis resulted in a 2.3 times greater risk of death.<sup>40</sup> However, an analysis of 14 924 patients with non-metastatic cancer treated with radiotherapy or chemoradiotherapy demonstrated that time till treatment start did not significantly affect survival, possibly because patients with more advanced disease were treated earlier.<sup>41</sup>

#### Time between surgery and radiotherapy

A longer than 4-week interval between surgery and radiotherapy was shown to impact negatively on recurrence-free survival but not overall survival.<sup>42</sup>

#### **Prostate tumours**

#### **Overall treatment time**

Some studies suggested that prostate cancers are relatively slow growing,43 and that delays of a few days may not significantly affect outcomes.44 Others suggested that delays may be more serious depending on tumour stage and radiation dose.45 An early study showed that radiotherapy treatment times of more than 9 weeks, compared to less than 7 weeks, had no effect on local control or survival of patients with T1c tumours. However, for patients with T2 localised tumours, local control and survival were inferior when treatment exceeded 9 weeks if the radiation dose was less than or equal to 72 Gy, but not if the radiation dose exceeded 72 Gy. No association between treatment time and outcome was found for T3 tumours.<sup>46</sup> In a retrospective study of 4839 patients, overall treatment times longer than 52 days had a significant effect on biochemical failure for patients treated with at least 70 Gy. A 1-week increase in treatment time was associated with a 6% increase in biochemical failure.47 A study

including 30% high-risk, 30% low-risk and 40% mediumrisk patients showed that those receiving doses of 74 Gy or more were not disadvantaged in terms of a 4-year biochemical failure by treatment extensions. However, for those receiving less than 74 Gy, a 15% increase in biochemical failure was observed if treatment was extended by 2 or more days.<sup>48</sup> In a recent study of 1728 patients, 113 patients with high-risk disease, it was found that four or more treatment interruptions did not significantly affect biochemical failure, metastasis or survival for those treated with at least 74 Gy.<sup>49</sup>

#### Tk and Dprolif

An analysis of clinical data from previous studies yielded an estimated Tk of 5–6 weeks, with a doubling time of 9–34 days.<sup>50</sup> In a more recent study, a similar Tk of 31 days, but a more rapid doubling time of 5 days, was estimated,<sup>51</sup> suggesting wide variability and potential differences in the impact of treatment delays.

*Dprolif* values of 0.24 Gy/day,<sup>47</sup> 0.34 Gy/day<sup>52</sup> and 0.52 Gy/day<sup>51</sup> were estimated. The latter *Dprolif* value suggests that some prostate cancers repopulate rapidly, being comparable to squamous cell carcinomas of the head and neck. Assumptions that prostate cancers are always slow growing and, thus, require less urgent treatment may be unfounded.

#### Time between prostatectomy and radiotherapy

For pT3 node-negative prostate cancer with undetectable prostate specific antigen (PSA) levels post-prostatectomy, patients are often offered either immediate adjuvant radiotherapy or PSA monitoring with salvage radiotherapy when there is biochemical failure. The latter approach allows patients who do not relapse to avoid potential side effects from radiotherapy. A retrospective study of 244 patients who received radiotherapy within 6 months of radical prostatectomy and 141 who received salvage radiotherapy later showed that metastasis-free survival and overall survival at 8 years were not significantly different.<sup>53</sup> Another retrospective study of 2190 patients suggested that delaying radiotherapy may even be beneficial, as it seemed to improve recovery from erectile dysfunction and urinary incontinence after surgery.<sup>54</sup> However, in a retrospective single institution study of 718 patients, although survival or metastasis rates were not different, 10-year biochemical failure was approximately 20% lower and freedom-from-androgendeprivation therapy was about 8% higher in men receiving immediate adjuvant radiotherapy.55

### Non-small cell lung cancer

#### **Overall treatment time**

There is evidence that delays during radiotherapy are detrimental.<sup>56,57</sup> An analysis of data from 1244 patients with unresectable non-small cell lung cancer (NSCLC) suggested that accelerated repopulation resulted in a loss of local control of about 1.7% per day for extensions beyond 3–4 weeks.<sup>58</sup>

Another study found that a cut-off of 45 days made a difference to local progression-free survival.<sup>59</sup> A retrospective analysis demonstrated that risk of death may increase by 2% per day for treatment prolongations of 5 days or more.<sup>60</sup> A more recent analysis of 14 154 patients with stage III NSCLC treated with concurrent chemoradiotherapy found that treatment delays significantly affected the overall survival. Median overall survival was reduced from 22.7 months for patients without delays to 18.6 months for patients with delays. A hazard ratio of 1.21 was estimated using multivariate analysis.<sup>61</sup>

#### Dprolif

A *Dprolif* value of 0.45 Gy/day was estimated for each day of treatment extension beyond 20 days.<sup>62</sup>

#### Time before radiotherapy

Clinical studies that have investigated the impact of delaying the initiation of radiotherapy on tumour response have yielded mixed results. Some studies suggest that delays may not affect outcome.<sup>63,64</sup> However, a small study of 29 lung cancer patients indicated that a median delay of 54 days between diagnosis and the start of radiotherapy resulted in 21% of potentially curable patients becoming incurable.<sup>65</sup>

Another study showed that 29% of patients became unsuitable for radical radiotherapy after treatment delays that resulted in the mean tumour volume increasing from 105 cc to 198 cc.<sup>66</sup> Some studies have shown that delaying the initiation of radiotherapy after chemotherapy may negatively affect outcomes, possibly as a result of chemotherapyinduced accelerated tumour cell proliferation.<sup>67,68</sup> There is also evidence that delays in initiating radiotherapy may have beneficial effects,<sup>69,70</sup> possibly because patients with more advanced disease were treated more promptly.

#### Small cell lung cancer

Concurrent chemoradiotherapy is the standard treatment for limited disease small cell lung cancer. Because chemotherapy may also initiate accelerated repopulation, it is possible that increased time between chemotherapy and thoracic irradiation initiation, in addition to prolonged overall radiotherapy treatment time, may be problematic.

#### Time between chemotherapy and radiotherapy

There is evidence that the time between chemotherapy and radiotherapy makes a difference. A systematic review and meta-analysis of seven randomised clinical trials using platinum-based chemotherapy with radiotherapy indicated that the 5-year survival rate was higher for those patients whose radiotherapy was initiated within 30 days of starting chemotherapy, with a hazard ratio of 0.65.<sup>71</sup> However, a phase 3 randomised trial did not show inferior survival and progression-free survival with delayed radiotherapy.<sup>72</sup>

#### **Overall treatment time**

An analysis of data from six trials that combined platinum or anthracycline-based chemotherapy with radiotherapy showed that patients who completed chemoradiotherapy more quickly had a superior 5-year survival rate, with a hazard ratio of  $0.6.^{73}$ 

#### Colorectal

#### **Overall treatment time**

In the Stockholm III trial, no difference in local recurrences, metastases, relapse-free survival or overall survival was observed when comparing  $5 \times 5$  Gy (EQD2 = 31.3 Gy) and  $25 \times 2$  Gy (EQD2 = 50 Gy).<sup>74</sup> The finding that tumour response was not better with the  $25 \times 2$  Gy regime is, possibly, evidence of repopulation occurring with this more protracted schedule.

#### Tk and Dprolif

In one study, accelerated repopulation was shown to occur but only in slowly proliferating tumours in female patients, with a Tk of about 4 weeks.<sup>75</sup>

In another study, *Dprolif* values for rectal cancer of 0.15 and 0.37 Gy/day were estimated.<sup>76</sup>

#### Time before radiotherapy

A prospective Danish study showed that delays of 60 days or more between diagnosis and radiotherapy were associated with a 69% inferior survival for patients with rectal, but not colon, cancer.<sup>77</sup> Subsequent studies, however, indicated that delays of up to 120 days<sup>78</sup> and even up to 100 weeks<sup>79</sup> did not affect survival in colorectal cancer patients.

#### Time between surgery and chemotherapy

Although not the main topic of this article, it is interesting to note that delays between surgery and chemotherapy in excess of 8 weeks<sup>80</sup> and 3 months<sup>81</sup> were associated with a significant reduction in survival.

#### Anus

#### **Overall treatment time**

A study that estimated the proliferation parameters of 22 squamous and four basaloid epidermoid carcinomas of the anus yielded a median potential tumour doubling time of 4.1 days.<sup>82</sup> This suggests that anal carcinomas may repopulate as rapidly as cervical carcinomas.

A retrospective analysis of 937 patients who had been part of Radiation Therapy Oncology Group (RTOG) trials 87–04 and 98–11 showed that overall chemoradiotherapy treatment times of more than 53 days resulted in inferior local control (hazard ratio [HR] 1.96), although the duration of radiotherapy *per se* did not affect tumour response.<sup>83</sup> Several smaller studies involving chemoradiotherapy indicated that treatment extensions are detrimental.<sup>84,85,86</sup> However, a retrospective analysis of 101 patients treated with chemoradiation demonstrated that a 5-year local control and colostomy-free survival rates were not adversely affected when treatment was interrupted by more than six cumulative treatment days, compared to six or less.<sup>87</sup>

#### Gliomas

#### Tk and Dprolif

From patients treated with surgery and radiotherapy, *Tk* values of 37 days<sup>88</sup> and 44 days<sup>89</sup> were estimated. *Dprolif* was estimated to be around 0.3 Gy/day.<sup>88,89</sup> The short tumour doubling time of 3 days estimated for high grade (III/IV) gliomas suggested that such tumours may have an even higher *Dprolif* (approximately 0.5 Gy/day) and are likely to be adversely affected by treatment extensions.<sup>90</sup>

#### Time between surgery and radiotherapy

**Delays worsen outcome**: An analysis of 345 patients given temozolomide and radiotherapy after surgery indicated that survival was significantly reduced if radiotherapy was initiated more than 6 weeks after surgery compared to 2 or less weeks.<sup>91</sup> A large retrospective study comprising 12 738 patients showed that there was a significant survival advantage when chemoradiotherapy was initiated less than 35 days after surgery.<sup>92</sup>

**Delays do not affect outcome**: Several recent studies, many of which included modern chemotherapy or chemoradiotherapy, could not show an effect of delaying the start of postoperative radiotherapy,<sup>93,94,95,96</sup> including a metaanalysis of 12 retrospective studies including 5212 patients.<sup>97</sup>

**Delays improve outcome**: A retrospective study of 2855 patients in the RTOG database found that delaying radiotherapy for a few weeks after surgery did not seem to affect survival and that an interval of more than 4 weeks improved survival. It was suggested that time may allow recovery from surgery-related brain damage and, possibly, reversal of postoperative hypoxia, which could influence tumour radiosensitivity.<sup>98</sup> A study of 2535 patients whose chemoradiotherapy was initiated within 13 weeks of surgery showed that those who waited at least 4 weeks before commencing radiotherapy had a better survival rate.<sup>99</sup> Starting radiotherapy within 3 weeks after surgery for paediatric medulloblastomas has been shown to have a negative impact on survival compared to when radiotherapy was started more than 3 weeks, but less than 90 days, after surgery.<sup>100</sup>

#### **Bladder tumours**

While radical cystectomy is a standard treatment for bladder cancer, transurethral resection followed by concurrent chemoradiotherapy yields a similar cure rate while maintaining bladder preservation.

#### **Overall treatment time**

Studies with 147 patients<sup>101</sup> and with 379 patients<sup>102</sup> showed that radiotherapy treatment prolongations did not affect local



Note: The reported studies were not performed by the authors but the Figure 1 representation of findings is the authors' own work. For more information, please refer to the reference list as indicated.

**FIGURE 1:** Tumours may be negatively affected by extensions in time to initiate treatment, by extensions in time between treatments and by extensions in the overall radiotherapy treatment time.

control. However, the relatively short estimated potential tumour doubling time of 3–8 days for bladder cancer suggests that treatment delays might adversely impact tumour response to radiotherapy.<sup>103</sup> In a small study, 2-year overall survival was 38% for patients who completed radiotherapy within 8 weeks, compared to 0% for those who completed their treatment over a longer period.<sup>104</sup> More recently, a study of 29 patients demonstrated a trend for treatment interruptions of more than 5 days to negatively affect survival.<sup>105</sup> The European Association of Urology has suggested that a course of radiotherapy should not extend beyond 6–7 weeks, so as to minimise the effect of repopulation.<sup>106</sup>

#### Tk and Dprolif

From a study that showed that local control was compromised by radiotherapy treatment extensions, it was estimated that the *Tk* for accelerated repopulation was about 5–6 weeks, with a *Dprolif* of 0.36 Gy/day.<sup>107</sup>

Overall, as summarized in Figure 1, extensions in therapy as a result of delays before or during treatment, or increased intervals between different modalities, may compromise treatment outcomes of many tumour types.

## Conclusions

Evidence for accelerated repopulation during therapy and cell division in the interval between diagnosis and initiating

treatment has been described in many tumour types. Therefore, it is important to avoid delays if possible and to compensate accordingly where relevant. All radiation oncology departments should have a policy on gaps and other treatment delays and be suitably informed as to how to assess treatment deviations and implement remedial action if warranted. Treatment waiting lists need to be periodically reviewed and the likely effects on outcomes assessed. Such information is useful to prioritise certain high-risk tumours or to motivate for increased resources or efficiencies where waiting times for treatment of highly proliferative tumours are found to be excessive.

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#### **Competing interests**

The authors have declared that no competing interest exists.

#### Authors' contributions

All authors contributed equally to this work.

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Data sharing is not applicable to this article as no new data were created or analysed in this study.

#### Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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