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Original Article

"Primer shot" fractionation with an early treatment break is theoretically superior to consecutive weekday fractionation schemes for early-stage non-small cell lung cancer

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ABSTRACT

Purpose: Radiotherapy is traditionally given in equally spaced weekday fractions. We hypothesize that heterogeneous interfraction intervals can increase radiosensitivity via reoxygenation. Through modeling, we investigate whether this minimizes local failures and toxicity for early-stage non-small cell lung cancer (NSCLC).
Methods: Previously, a tumor dose-response model based on resource competition and cell-cycle-dependent radiosensitivity accurately predicted local failure rates for early-stage NSCLC cohorts. Here, the model mathematically determined non-uniform inter-fraction intervals minimizing local failures at similar normal tissue toxicity risk, i.e., iso-BED3 (iso-NTCP) for fractionation schemes 18Gyx3, 12Gyx4, 10Gyx5, 7.5Gyx8, 5Gyx12, 4Gyx15. Next, we used these optimized schedules to reduce toxicity risk (BED3) while maintaining stable local failures (TCP).
Results: Optimal schedules consistently favored a "primer shot" fraction followed by a 2-week break, allowing tumor reoxygenation. Increasing or decreasing the assumed baseline hypoxia extended or shortened this optimal break by up to one week. Fraction sizes of 7.5 Gy and up required a single primer shot, while smaller fractions needed one or two extra fractions for full reoxygenation. The optimized schedules, versus consecutive weekday fractionation, predicted absolute LF reductions of 4.6%-7.4%, except for the already optimal LF rate seen for 18Gyx3. Primer shot schedules could also reduce BED3 at iso-TCP with the biggest improvements for the shortest schedules (94.6Gy reduction for 18Gyx3).
Conclusion: A validated simulation model clearly supports non-standard "primer shot" fractionation, reducing the impact of hypoxia-induced radioresistance. A limitation of this study is that primer-shot fractionation is outside prior clinical experience and therefore will require clinical studies for definitive testing.

Introduction

The use of hypofractionation and stereotactic radiotherapy is increasing for all cancers. In breast[1] and prostate cancer[2], schedules have been reduced to 5 fractions. Similarly, hypofractionation is ideal for many early-stage non-small-cell lung cancer (NSCLC), given the small amount of lung tissue in the irradiated volume[3]. The resulting local failure (LF) rate is low, especially for peripherally located tumors [4] that can receive more effective fractionation regimes, typically to biologically effective doses (BED) of $>$ 100 Gy [5]. However, when tumors are closer to organs at risk (OARs), these high doses are often not possible. This is most pronounced in ultra-central tumors as their proximity to the proximal bronchial tree, trachea, esophagus, heart, or great vessels can lead to treatment-related, possibly fatal, toxicities. Lowering the fraction size reduces this morbidity risk but can simultaneously increase LFs[6–9].

Radiobiological modeling has been dominated by the linear-quadratic (L-Q) paradigm for the last 40 years. In this framework, tumor response is expected to scale according to simple parameters derived from data that putatively describe tumor cell response to

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multifractional irradiation in vitro[10]. Efforts to use computer modeling to understand whether non-uniform fractionation schemes could enhance radiotherapy response go back at least to Cohen's kinetic models that stimulated later clinical trials[11,12]. However, those models did not account for now well-known radiobiological phenomena, such as the resolution of hypoxia over a course of radiotherapy[13].

Recently, we have developed a more comprehensive mathematical approach to simulating the time course of tumor response to radiotherapy[14,15]. The model simulates radiobiologically-important phenomena, including cellular competition for limited oxygen and glucose, cell-cycle-dependent radiosensitivity, hypoxia-induced radioresistance, radiation-induced cell-kill, and proliferation[14]. With this model, we were able to validate a tumor control probability (TCP) calculation for early-stage NSCLC tumors across all published fractionation cohorts, including in set aside validation cohorts[15]. Nearly all those cohorts used evenly spaced weekday fractionation schemes (e.g., every weekday, 3 fractions per week, etc.). However, the microenvironmental conditions of a tumor are known to evolve, with hypoxia often resolving in the early weeks of radiotherapy as determined through imaging and oxygen probes[16–18]. This effect, along with common mass and volume loss observed in regressing tumors[19], means that the biological effect of a fraction is unlikely to be consistent throughout a treatment course. This motivates the unanswered question: whether a non-standard fractionation approach is predicted to be significantly more effective, holding to a similar normal tissue impact, than the regimes studied to date. Surprisingly, we find a clear, positive, and easily explainable answer to this question.

We briefly review the basis of the tumor simulation model. The model was designed to capture well-established radiobiological phenomena such as the competition for oxygen, the ability of cells to take up glucose even in the absence of oxygen, and the high loss rate of daughter cells that the tumor cannot support. Cells are mathematically distributed across three cellular compartments: proliferating cells (P-compartment) with access to oxygen and glucose, hypoxic cells (H-compartment) with access to glucose but not oxygen, and starving cells (S-compartment) without access to oxygen or glucose (compartments are renamed from the original paper for greater clarity). The model postulates that cells in the P-compartment progress through the cell cycle. Cell loss before therapy takes place in the nutrient-deprived S-compartment. Cells in the H-compartment are metabolically viable and neither die nor proliferate. Treatment fractions cause cell death through mitotic catastrophe, reducing oxygen consumption and thereby allowing hypoxic cells to access oxygen, thus modeling reoxygenation.

In this paper, we report our validated mechanistic and empirical tumor-response model, investigating novel fractionation schemes for NSCLC. These optimized fractionation schedules are designed to either reduce LF without increasing toxicity (*iso*-NTCP) or reduce dose/toxicity without increasing LF (*iso*-TCP).

Methods

The tumor-response model[15] can be used to compare the effect of temporal variations of radiotherapy fractions on the tumor cell survival or treatment efficacy. The model can find for each schedule the model-derived equivalent dose, normalized for a weekday radiotherapy schedule (2 Gy/weekday), which then translates to a tumor cell survival and LF rate via the dose–response curve. Reoxygenation and proliferation are modeled in the S, H, and P-compartments, whose starting sizes are determined by the growth fraction (GF) and the tumor doubling time (T_D). GF directly determines the size of the P-compartment and the higher the GF is, the larger the P-compartment is. The relative sizes of the remaining H- and S-compartments are determined by T_D. For more details, please see references 14 and 15. A higher GF reflects a more proliferating tumor with a larger P-compartment and smaller H and S-compartments. Through this, the GF determines the reoxygenation time and effectiveness of a radiotherapy schedule.

Six common fractionation schedules for peripheral and (ultra-)central early-stage NSCLC (18Gyx3, 12Gyx4, 10Gy×5, 7.5Gy×8, 5Gyx12, 4Gy×15) were considered for simulated optimization. Intervals between fractions were varied independently to find the schedule with the lowest simulated tumor cell surviving fraction. Using a grid search, for the schedules with 3–5 fractions, all possible intervals were tested within 5 weeks of treatment. For the longer schedules, to make the search more feasible, the first 6 fractions were optimized ("reoxygenation phase"), followed by consecutive weekday fractions in the second phase.

First, we only varied the interfraction intervals, keeping the original fraction size, and compared the LF rates between the optimal schedule and the consecutive weekday fractionation schedule (5 fractions/week). This analysis is *iso*-NTCP, as the total normal tissue biologically effective dose for late toxicity (BED_3) was necessarily constant, as it is independent of fraction spacing.

In a second analysis on late toxicity, we also varied the fraction size next to the interfraction intervals. As the optimal schedule found in the previous analysis improves the treatment efficacy, we could lower the fraction size keeping the same LF and this lowers the normal tissue BED_3. The physical fraction size was decreased until the cell survival and thus LF of the optimal schedule becomes equivalent to that of consecutive weekday fractionation ('*iso*-TCP'). In other words, the optimized schedule compensated for the potential LF increase of the radiotherapy dose reduction. In this *iso*-TCP analysis, BED_3 of the target volume treatment was used as a reference for toxicity. This is a simplification, as toxicity for given endpoints depends differentially on fractionation and the volume of high dose regions[20]. Nonetheless, BED_3 shows how an optimization of the treatment intervals could allow reductions in effective normal tissue doses without increasing LFs.

A key parameter of the model impacting the rate of reoxygenation is the GF, quantifying the fraction of cells in the proliferative compartment, having access to enough oxygen and glucose to progress through the cell-cycle. The GF used in the original tumor-response model (0.25) was the average value in a NSCLC cohort based on in vivo labeling[21]. However, tumors differ in hypoxia and proliferation. This motivated parametric testing to see how individual variations in GF impact the optimality of the schedules. We analyzed the influence of GF variations (GF of 0.2, 0.25, and 0.3) on the identified optimal schedule, the *iso*-NTCP LF rate reduction, and the *iso*-TCP BED_3 (late toxicity) reduction. As the GF controls the starting cell distribution in the compartments, a smaller GF (e.g., 0.2 vs. 0.25 used as standard) translated to less proliferating and more hypoxic and starving cells, thus increasing the reoxygenation time and therefore influencing the best performing schedule. Finally, we calculated LF rates for cases when the schedule is based on an incorrect assumption of the GF. As an exploratory analysis, we calculated the LF reductions when using the schedule optimized for GF 0.25 for tumors with GF 0.2 and 0.3. All analyses were done in Matlab version 9.7 [22] and RStudio version 2022.02.3[23].

Results

For consecutive weekday fractionation (5 fractions/week), LF rates for 18Gyx3, 12Gyx4, 10Gy×5, 7.5Gy×8, 5Gyx12, and 4Gy×15 were calculated to be 5.4 %, 10.3 %, 12.6 %, 11.5 %, 14.3 %, and 14.3 %, respectively (see Fig. 1). Increasing the GF from 0.25 to 0.3 (increasing proliferation) lowered the LF rate, especially for schedules with more fractions. In contrast, a GF decrease from 0.25 to 0.2 (enhancing hypoxia) resulted in a higher LF rate. This effect was again stronger for longer schedules (Supplementary table 1).

For each optimized fractionation scheme, the schedule with the lowest cell survival and LF rates had two phases (see Fig. 2). For the standard GF value of 0.25 and fraction sizes of 7.5 Gy and up, the first hypoxic or radioresistant phase consisted of one fraction followed by a break of 2 weeks, during which hypoxic cells were eliminated due to reduced competition for resources (i.e., reoxygenation) (see Table 1). Below 7.5 Gy per fraction, the duration of break remained the same (2

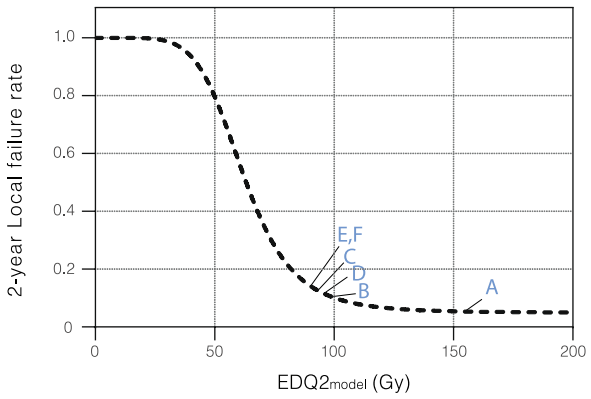

Fig. 1. Local failures for consecutive weekday fractionations for 18Gyx3 (A), 12Gyx4 (B), 10Gyx5 (C), 7.5Gyx8 (D), 5Gyx12 (E), and 4Gyx15 (F).

weeks) but a second fraction was required halfway through the break to ensure reoxygenation. Following the break, the tumor enters a normoxic or radiosensitive phase, with the entire tumor assumed to be in the oxygen and glucose rich compartment. Thereafter, completing radiotherapy as quickly as possible is optimal, and consecutive weekday fractionation performs best. These optimized schedules are hereafter named "primer shot" schedules. With a higher GF of 0.3, the optimal break for reoxygenation decreased to 1 week, whereas with a GF of 0.2, the optimal break increased to around 3 weeks (see Supplementary Table 1). Furthermore, the combination of a GF of 0.2 and a fraction size under 7.5 Gy necessitated 3 fractions during the 'break' interval for reoxygenation.

The optimized primer shot schedules reduced LF rates without increasing the total dose or assumed toxicity (*iso*-NTCP). For 18Gyx3, the LF rate with weekday fractionation was within 0.3 % of the rate with the primer shot, as the LF was already in the saturated region of dose response curve. However, for the other schedules this predicted improvement was much higher: 4.6 %-6.6 % (see Fig. 3). Assuming more hypoxic tumors with a GF of 0.2, the impact of the primer shot schedule was even greater, especially for the longest two schedules: 20.1 % absolute increase in TCP for 5Gyx12 and 21.3 % for 4Gy×15 (see Supplementary Fig. 1A). Assuming a more proliferative tumor, with a GF of 0.3, the TCP gains were more modest (see Supplementary Fig. 1B).

The same optimized primer shot schedules could also reduce late

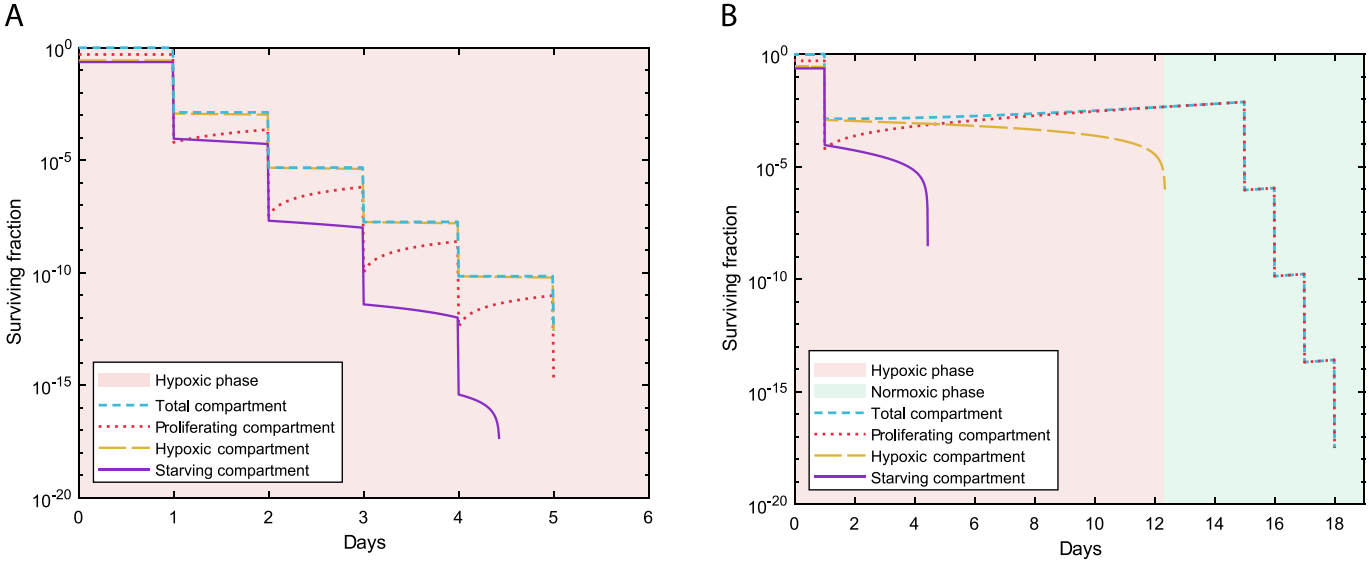

Fig. 2. Effect of fractionated radiotherapy (10Gyx5) on cell survival in the compartments (for GF 0.25). (A) With consecutive weekday fractionation (5 fractions/week), the hypoxic compartment is still present at the last fraction, reducing the radiosensitivity according to the OER. (B) The optimal primer shot schedule delivers 1 primer fraction followed by a 2-week break. Reoxygenation following mitotic cell death shrinks the hypoxic and starving compartments. Even though proliferation increases the tumor cells, the increased radiosensitivity has a much stronger effect on the final cell survival, resulting in a local failure reduction (6% vs 12.6%). Note that the new fraction does not start immediately after reoxygenation due to the weekend break.

Table 1
Optimal primer shot schedules (fractions in dark grey) for a GF of 0.25 with corresponding local failure rates vs consecutive weekday fractionation. LF = local failure.

Schedule	LF weekday	LF primer	WEEK 1					WEEK 2					WEEK 3					WEEK 4					WEEK 5				
			M	T	W	R	F	M	T	W	R	F	M	T	W	R	F	M	T	W	R	F	M	T	W	R	F
18Gyx3	5%	5%																									
12Gyx4	10%	6%																									
10Gyx5	13%	6%																									
7.5Gyx8	12%	6%																									
5Gyx12	14%	7%																									
4Gyx15	14%	9%																									

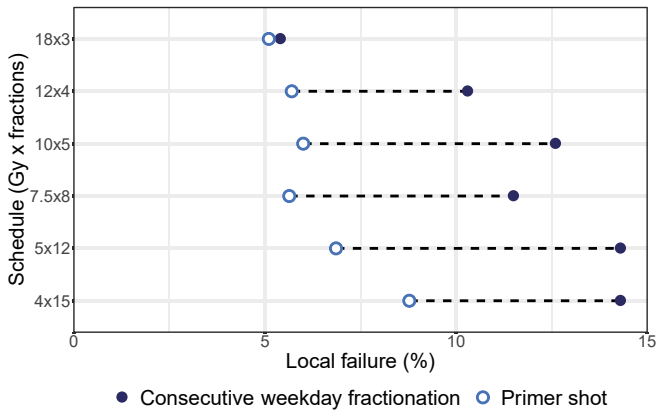

Fig. 3. Iso-NTCP reductions for local failure rate with primer shot vs consecutive weekday fractionation for a GF of 0.25.

toxicity without increasing LFs (*iso*-TCP). By reducing the physical fraction size of the optimal primer shot schedules, the BED_3 was reduced for all optimal schedules, with the largest reduction for the three shortest schedules (see Fig. 4). Changes in GF primarily affected the longer schedules. The BED_3 reductions were larger for more hypoxic tumors (GF 0.2 vs 0.25) and smaller for more proliferating tumors (GF 0.3 vs 0.25) (see Supplementary Fig. 2A and 2B).

Inaccurately predicted GFs reduced the benefit of the primer shot. For example, an optimal primer shot schedule assuming a GF of 0.25, when the actual tumor is more hypoxic with GF of 0.2, suggests a 2-week break instead of the ideal 3 weeks for such a tumor. The impact of such proliferation overestimation was not negligible, with a predicted loss of up to 4.8 % in absolute TCP (see Supplementary Fig. 1C). However, underestimations of proliferation resulted in insignificant reductions in efficacy, smaller than 1 % (see Supplementary Fig. 1D and Supplementary Table 1 for all TCPs).

Discussion

Radiotherapy fractionation schemes have mostly consisted of equispaced weekday fractionation. The validated simulation model allows the exploration of the optimal inter-fraction separations. It implies that "primer shot" schedules provide an improvement in radiobiological effect, leveraging the known radiobiological effect of hypoxia and reoxygenation, which has been well established, for example, via [^{18}F]-fluoromisonidazole (FMISO) Positron Emission Tomography (PET) imaging[18]. The simulation model implies that a better fractionation schedule would consist of "priming" the tumor to doom most cells in the proliferative compartment to begin the roughly two-weeks-long process of reducing the fraction of hypoxic cells. The optimal course has a complete break after an initial fraction of 7.5 Gy or larger. The optimal break is predicted to be 2 weeks for the population assumed value of GF (0.25), but in fact may vary for strongly proliferative (1 week break is optimal if GF is 0.3), or strongly hypoxic tumors (3 week break is optimal if GF is 0.2). If the fraction size is smaller than 7.5 Gy, one or two extra primer fractions are needed over the break to achieve full reoxygenation. The primer shot leads to increased radiotherapy efficacy in the second, radiosensitive phase of the schedule by simply eliminating radioresistant tumor cells before delivering most of the radiation dose. Primer-shot schemes could significantly improve the treatment for patients with unfavorable NTCP and TCP tradeoffs, as in the case of early stage ultra-central NSCLC.

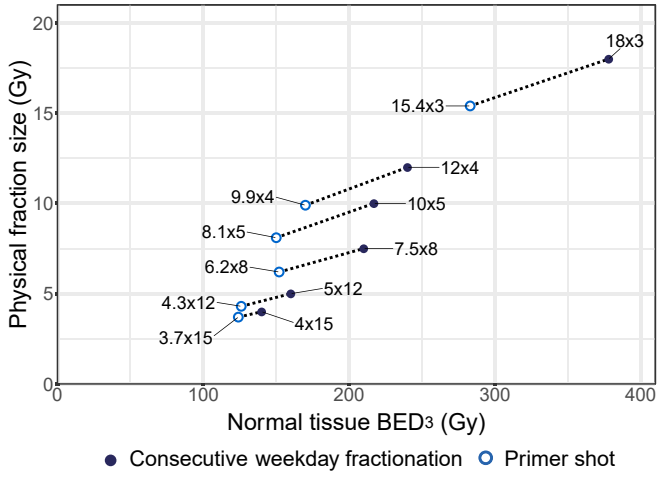

Fig. 4. Primer shot *iso*-TCP reductions for late toxicity biologically equivalent dose (BED_3) for a GF of 0.25. Compared with consecutive weekday fractionation, the optimized primer shot schedule is used to lower the BED_3 while maintaining a constant LF rate.

It is important to note that the predicted TCP increases with primer shot depend on the dose–response curve. Primer shot consistently increases radiotherapy efficacy, measured in our model as the $EQD2_{model}$ (for GF 0.25 from 17.5 % (for 4Gyx15) up to 49.1 % (for 7.5Gyx8), see Supplementary Table 1). However, the resulting TCP increases depend on the starting position on the dose–response curve, as increased efficacies translate to far stronger TCP increases on the steep part of the curve. This effect is particularly prominent for 18Gyx3, whereby primer shot is predicted to increase $EQD2_{model}$ by 34 %, but results in almost no TCP increase due to starting in the saturated region of the dose–response curve.

Treatment breaks are tested as split-courses, hypothesizing they selectively spare normal tissues vs tumor cells[24]. Treatments were typically interrupted during the second half of a 5–9-week course with conventional fraction sizes close to 2 Gy. They fell out of favor after a retrospective analysis showed that split course for larynx cancer failed to improve tumor control despite the 12 Gy higher dose and let to more late toxicity [25]. However, these results should not lessen the confidence in a primer shot schedule. Our model predicts efficacy improvements of early breaks in hypofractionated treatments, but a detrimental effect of late breaks during the reoxygenized, second phase. This is consistent with repopulation-induced efficacy reductions of fractions delivered after 28 or more days of overall treatment time[14,26]. Recently, a promising preclinical study[27] showed that increasing the time interval of stereotactic radiotherapy fractions could increase the synergy of radiotherapy and immunotherapy. Even though the following clinical trials explore an important question, this question is different from primer shot. Whereas the abovementioned Pulsar-regimen implements equal-spaced intervals to promote immune response, primer shot is intended to implement heterogeneous interfraction intervals to combat hypoxia-induced radioresistance.

Our model focuses on chronic, diffusion-limited tumor hypoxia, caused by the limited oxygen supply from the surrounding vasculature [28]. As tumor cells reduce during fractionated radiotherapy, more oxygen becomes available for the remaining cells, reducing hypoxic and resistant cells. Based on this, hypoxia impacts mainly the shorter, hypofractionated courses as longer courses benefit from inherent reoxygenation. Primer shot minimizes the required dose for reoxygenation while maximizing the dose delivered in the oxygen-rich phase with increased tumor radiosensitivity. It is true that tumor cell proliferation also reduces dose effectiveness, as identified by many investigators [25,26,29]. This reduced efficacy in the abovementioned studies is however primarily shown for schedules with low fraction sizes (close to 2 Gy) and long overall treatment times. Our model confirms this observation as prolonging the overall treatment time for schedules with 2 Gy fractions was detrimental (data not shown). However, in hypofractionated treatments, the consequences of proliferation and overall treatment time prolongation are smaller than the expected impact of

hypoxia, translating to the suggested benefit of the primer shot schedule.

In the late toxicity or *iso*-TCP analysis, we conservatively only considered 'toxicity' reductions from lowering the BED_3. This simplification approximates the potential dose reductions without increasing LFs. However, the effect on toxicity depends on dose distributions, the proximity to OARs and the NTCP models, this needs clinical validation. The effect is more likely to be relevant for central tumors close to, for instance, the bronchial tree and the great vessels. Next to dose reductions, primer shot could reduce toxicities via the increased overall treatment time. This is more likely if the tissue recovery time is comparable to the primer shot break length. This is the case for acute toxicities, for instance, a radiotherapy break of 10 days activated the mucosa and decreased mucositis[30]. However, late toxicities are unlikely to be influenced as the recovery times are much longer, months to years [31]. For the late toxicities, one should focus on reducing the radiotherapy dose through primer shot schedules.

Our results show the importance of accurately predicting the proliferation and hypoxia of a tumor as these properties decided the optimal primer shot break length. Applying a suboptimal primer shot break reduced the benefits. Integrating imaging could personalize the primer shot fractionation schedule and optimize its benefits. The important measurement of hypoxia can be done by imaging and a prior modeling study showed that previously published imaging biomarkers seem consistent with model results[32]. The first option would be to calculate tumor growth by comparing the diagnostic Computed Tomography (CT) to the radiotherapy planning CT; this has already been shown to be prognostic in oropharyngeal cancer[33] and NSCLC[34]. A second option is to use functional imaging to predict the starting distributions of the proliferating and hypoxic compartments. For instance, FMISO PET is a surrogate for hypoxia[35] and [^{18}F]-fluoro-3′-deoxy-3′-L-fluorothymidine (FLT) PET can measure proliferation[36]. A third option would correlate changes in image-based biomarkers such as total mass loss from in-Tx-room cone-beam CT or apparent diffusion coefficient data from MRI, to adaptively decide on the length of the break.

Our study has significant limitations. First, although our mechanistic tumor response model accurately predicted tumor control across all previously published NSCLC fractionation regimens, these cohorts did not receive primer shot schedules. We are cognizant of the increased estimation uncertainties of extrapolations beyond fitted data. Yet, our model is not purely empirical, but also mechanistic and built on well-established radiobiological processes that should hold validity for new regimens. Currently, our model is limited to early-stage NSCLC. However, the mechanism is not dependent on the NSCLC-specific parameters, and expanding the model to other disease sites and stages would increase its impact. Also, the model currently calculates the treatment effect of the tumor cells individually as they move through the compartments. Including spatial heterogeneity would be an improvement, incorporating the local metabolic conditions of neighboring tumor cells. Lastly, we compared primer shot to consecutive weekday fractionation (5 fractions/week), but hypofractionation with large fraction sizes is often given 2–3 times a week. According to our model, the influence of these limited and homogeneous interfraction time prolongations is very small (data not shown). Nonetheless, any clinical trial should compare primer shot against the standard practice.

In summary, the mechanism of reoxygenation implies that giving a treatment break after a first ("primer") fraction could lead to significantly improved efficacy against tumors compared to previously tested regimens. Preclinical studies and clinical studies using imaging correlates (like diffusion-weighted MRI, FMISO PET, or FLT PET, during and after treatment) would be rational ways to test these predictions.

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CRediT authorship contribution statement

Z.A.R. Gouw: Formal analysis, Investigation, Methodology, Writing – original draft. **J. Jeong:** Formal analysis, Investigation, Methodology, Writing – review & editing. **A. Rimner:** Writing – review & editing. **N.Y. Lee:** Writing – review & editing. **A. Jackson:** Methodology, Writing – review & editing. **A. Fu:** Writing – review & editing. **J-J. Sonke:** Writing – review & editing. **J.O. Deasy:** Funding acquisition, Supervision, Writing – review & editing.

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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2023.110006.

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