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ORIGINAL ARTICLE

Prolonged Fraction Duration Reduces Tumoricidal Efficacy in a Breast Cancer Cell Line: A Simulated Model of Gated Radiotherapy

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OBJECTIVE

Respiratory-controlled radiotherapy (breath-hold and gating) reduces cardiac exposure in breast cancer but prolongs and fragments intrafraction delivery, lowering the effective dose rate, an effect that is accentuated when patient compliance is imperfect. We tested whether prolonging the delivery of a single 2 Gy fraction compromises tumoricidal efficacy in breast cancer cells, independent of total dose.

METHODS

Michigan Cancer Foundation-7 (MCF-7) cells received 2 Gy delivered rapidly and continuously (reproducing tangential treatment) or as intermittent pulses over 10 or 20 min (reproducing gating), with a non-irradiated control. Viability was assessed by WST-1 at 24 and 48 h, and DNA double-strand break signaling by γH2AX immunofluorescence and flow cytometry (γH2AX and phospho-ATM [pATM]) at 6, 12 and 24 h.

RESULTS

Continuous delivery produced the lowest viability, significantly below control at 24 h (81.2%, p=0.0072) and 48 h (79.7%, p=0.0047); viability rose with delivery time (24 h: 88.4% and 93.3% for 10 and 20 min). Immunofluorescence γH2AX foci were highest after continuous delivery and decreased with delivery time, exceeding control at all-time points. Flow-cytometric γH2AX and pATM were biphasic (peak 6 h, nadir 12 h, rise 24 h), with continuous and 10-min groups above control and fewest undamaged cells after continuous delivery.

CONCLUSION

Prolonging fraction delivery reduced tumoricidal efficacy in MCF-7 cells, consistent with sublethal damage repair at lower, pulsed dose rates. Intrafraction delivery time is a potentially modifiable parameter that warrants consideration when gating or breath-hold extends beam-on time.

Keywords: Breast neoplasms; cell survival; DNA damage; dose-response relationship; radiation; gated radiotherapy, histones (γH2AX).

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INTRODUCTION

Breast cancer is the most frequently diagnosed cancer in women worldwide,[1] and radiotherapy is integral to its locoregional management, reducing recurrence and improving survival.[2] These gains are tempered by a recognized risk of late cardiac toxicity. The risk of ischemic heart disease rises with the mean heart dose, by approximately 7.4% per gray in the analysis of Darby et al.[3] and by about 4% per gray as estimated by Sardaro et al.,[4] and the contribution of radiotherapy to non-cancer mortality has been confirmed in modern dose- and trial-based analyses.[5]

To limit cardiac exposure, respiratory-controlled techniques (deep inspiration breath-hold and respiratory gating) have become standard for left-sided breast irradiation, exploiting displacement of the heart away from the chest wall during deep inspiration to lower heart dose.[6,7] Their effectiveness, however, depends on the patient consistently reproducing the target respiratory phase. In conventional tangential treatment, the prescribed dose is delivered rapidly and without interruption (continuous delivery). Under gating, by contrast, the beam is enabled only during the appropriate part of the breathing cycle, so that delivery becomes intermittent; when patient compliance is imperfect, due to anxiety or an irregular breathing pattern, the correct respiratory window is harder to capture and the beam-on time can be substantially prolonged.[7]

Prolonging and fragmenting the delivery of a fixed dose lowers the effective dose rate and converts a single rapid exposure into a series of pulses. Dose rate is an established modifier of radiobiological effect: at lower dose rates, sublethal damage repair operating during irradiation can reduce cytotoxicity.[8–11] Consistent with this, *in vitro* and modeling studies of protracted delivery have reported increased clonogenic survival and a reduced biological effect as delivery time lengthens.[12–16] This raises a clinically important concern, that the very prolongation introduced to spare the heart might, in some patients, diminish the tumoricidal effect on breast cancer cells, yet this scenario has not been examined in a cell-culture model that reproduces gated delivery one-to-one.

To address this gap, we developed an *in vitro* model that simulates the range of beam-on times encountered in practice. A single 2 Gy dose was delivered to Michigan Cancer Foundation-7 (MCF-7) breast cancer cells under three schedules: a rapid, uninterrupted (continuous) exposure reproducing conventional tangential treatment; an intermittent delivery over 10 min representing a compliant gated patient; and an intermittent delivery over 20 min representing a patient with greater difficulty maintaining the gating window. Cell viability and the DNA double-strand break response were assessed, using γH2AX, a sensitive and specific marker of double-strand breaks,[17,18] together with phospho-ATM (pATM), to determine whether prolonged, intermittent delivery compromises tumoricidal efficacy.

MATERIALS AND METHODS

Cell Culture

The human breast cancer cell line MCF-7 was cultured in RPMI 1640 with high glucose, supplemented with 10% fetal bovine serum and 1% penicillin, at 37°C in a humidified atmosphere with 5% CO_2. At 80–90% confluence, cells were subcultured with 0.5% trypsin-EDTA according to the manufacturer's protocol, resuspended in fresh medium, and seeded onto sterile plates. Cells were incubated for 24 h before irradiation to allow attachment.

Irradiation and Experimental Groups

Irradiation was performed with a TrueBeam STx linear accelerator (Varian Medical Systems, Palo Alto, CA, USA) using 6 MV photons at a source-to-surface distance of 100 cm over a 20×20 cm field, at a single fraction dose of 2 Gy. Delivery schedules were modeled on breast cancer patient treatment plans with the assistance of a medical physicist to reproduce, at the cellular level, the beam-on profiles encountered in clinical practice. Four groups were studied (Fig. 1): A non-irradiated control; a continuous group, in which 2 Gy was delivered rapidly and without interruption to simulate conventional two-field tangential breast irradiation (the beam itself was brief; the total time on the machine was approximately 1 min and was attributable to gantry rotation between the two tangential fields rather than to protraction of the dose); an intermittent group, in which the same 2 Gy was delivered as interrupted beam pulses over a total of 10 min to simulate a compliant patient treated with respiratory gating; and a second intermittent group, in which 2 Gy was delivered over 20 min to simulate a patient with greater difficulty maintaining the gating window. The control was handled identically and transported alongside the irradiated groups.

Cell Viability (WST-1 Assay)

Cells were seeded at 5×10^3 cells/100 µL per well in 96-well plates. At 24 and 48 h after irradiation, 10 µL/well of WST-1 reagent (ScienCell Research Laboratories, Carlsbad, CA, USA) was added and the plates were

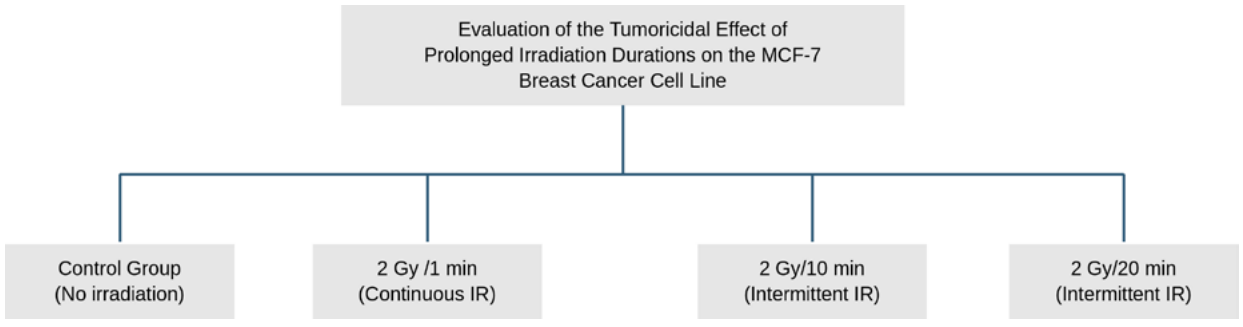


Fig. 1. Experimental groups and irradiation protocol. Michigan Cancer Foundation-7 cells received 2 Gy delivered rapidly and continuously (simulating conventional tangential treatment), or as intermittent pulses over 10 or 20 min (simulating respiratory gating), with a non-irradiated control.

incubated for 2 h at 37°C. Absorbance was measured at 450 nm on a microplate spectrophotometer (Thermo Scientific, Waltham, MA, USA). Viability was expressed as a percentage of the time-matched control.

γH2AX Immunofluorescence

At 6, 12 and 24 h after irradiation (1×10^4 cells per coverslip in 12-well plates), cells were fixed in 4% formaldehyde for 15 min at room temperature, washed with PBS, and blocked with Super Block protein blocking reagent (ScyTek Laboratories, Logan, UT, USA) for 60 min. Coverslips were incubated overnight at 4°C in a humidified chamber with anti-phospho-histone H2A.X (Ser139) primary antibody (1:200), then for 1 h at room temperature with a Texas Red-X-conjugated goat anti-mouse IgG secondary antibody (1:500). Nuclei were counterstained with DAPI-containing mounting medium, and slides were imaged by fluorescence microscopy at ×100. γH2AX foci were quantified with ImageJ.

γH2AX and pATM flow Cytometry

The DNA damage response was assessed with the Muse Multi-Color DNA Damage Kit (MCH200107, Luminex, Austin, TX, USA) according to the manufacturer's protocol. At 6, 12 and 24 h after irradiation (3×10^5 cells per well in 6-well plates), cells were harvested with trypsin, fixed and permeabilized, and stained with anti-pATM (Ser1981)-PE and anti-phospho-histone H2A.X (Ser139)-PECy5 for 30 min at room temperature in the dark. After washing, cells were resuspended in assay buffer and analyzed on a Muse Cell Analyzer.

Statistical Analysis

Analyses were performed in GraphPad Prism v8 (GraphPad Software, Boston, MA, USA). Data are presented as mean±standard deviation of at least three independent experiments. Normality and homogeneity of variance were checked before parametric testing. Differences between groups were evaluated by two-way ANOVA (factors: Irradiation group and time), with Dunnett's post hoc test comparing each irradiated group with the control. $P<0.05$ was considered statistically significant.

RESULTS

Experimental Design and Included Data

Several independent experiments were performed. Experiments with protocol deviations affecting the control group – those in which the control was not transported to the irradiation area together with the other groups, or in which plates were not collected at the prescribed time after preparation – were excluded. The analyses below are based on the experiments in which all four groups, including the control, were prepared, transported, and irradiated under identical conditions.

Continuous Delivery Produced the Greatest Loss of Cell Viability

WST-1 viability showed a consistent, delivery-time-dependent pattern at both time points. Relative to the time-matched control (set to 100%), viability at 24 h was 81.2% for the continuous (tangential) group, 88.4% for the intermittent 10-min group, and 93.3% for the intermittent 20-min group; at 48 h, the corresponding values were 79.7%, 89.8%, and 96.0%. Viability increased monotonically with delivery time at both time points, with the 20-min group closest to control levels; the continuous group was the only group significantly below control (24 h, $p=0.0072$; 48 h, $p=0.0047$), whereas neither intermittent group differed significantly from control. The ordering was preserved between 24 and 48 h, indicating a stable rather than transient effect (Fig. 2).

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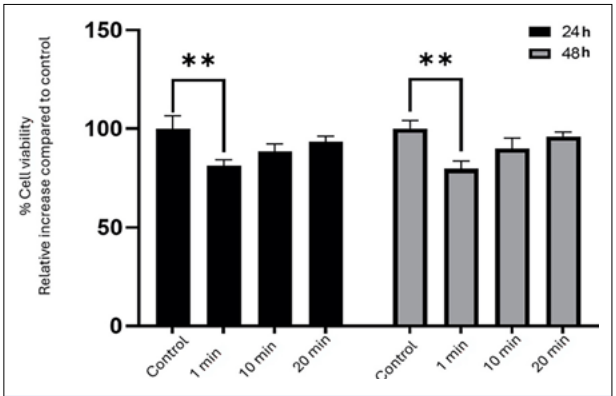


Fig. 2. Cell viability (WST-1) at 24 and 48 h, expressed as a percentage of the time-matched control. Only continuous delivery was significantly below control (**p<0.01); viability increased with delivery time. Bars show mean±standear deviation.

γH2AX foci by Immunofluorescence Decreased as Delivery Time Increased

All irradiated groups contained markedly more γH2AX foci than control at every time point (p<0.05), and the number of foci decreased monotonically from the continuous group through the 10-min to the 20-min group. Foci counts (total per 50 analyzed cells) for the control, continuous, 10-min and 20-min groups were 118, 277, 262, and 248 at 6 h; 113, 266, 251, and 240 at 12 h; and 98, 205, 187, and 162 at 24 h, respectively. Irradiated groups thus carried approximately twice the foci burden of control, with the continuous group consistently highest. In every group, foci declined from 6 to 24 h, consistent with progressive resolution of double-strand breaks, while a low background level of foci persisted in the non-irradiated control (Table 1; Figs. 3, 4).

γH2AX and pATM by Flow Cytometry

Flow cytometry quantified the proportions of undamaged (negative) cells and of γH2AX- and pATM-positive cells. The proportion of undamaged cells was lowest after continuous delivery and highest in the control at every time point (e.g., 58.4% vs. 82.2% at 24 h), with the intermittent 10-min and 20-min groups intermediate, indicating that the greatest DNA damage occurred after continuous delivery. Both γH2AX and pATM followed a biphasic time course, with the signal highest at 6 h, declining at 12 h and rising again at 24 h. Across the 3 time points, the continuous and intermittent 10-min groups were significantly increased relative to

Table 1 γH2AX foci counts (total per 50 analyzed cells) by irradiation group and time point

Group	6h	12h	24h
Control	118	113	98
Continuous (tangential)	277	266	205
Intermittent, 10 min	262	251	187
Intermittent, 20 min	248	240	162

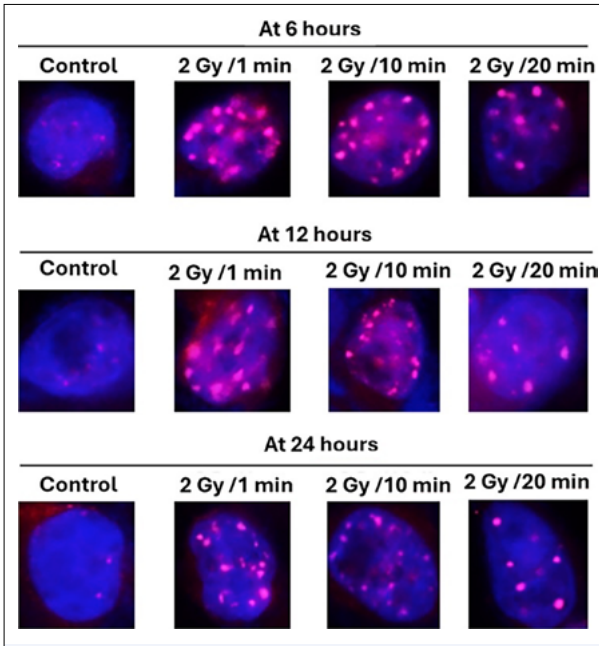


Fig. 3. Representative fluorescence microscopy images of γH2AX foci (red) and DAPI-stained nuclei (blue) across groups and time points.

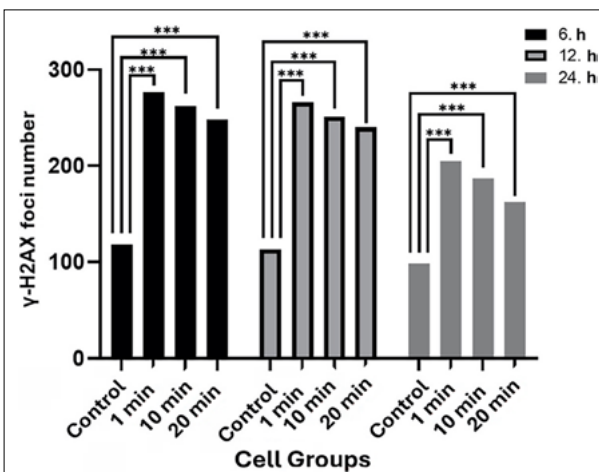


Fig. 4. Quantification of γH2AX foci (total per 50 cells) over time. Foci were highest after continuous delivery and decreased with longer delivery time; all irradiated groups exceeded control at every time point (p<0.05).

control ($p<0.05$), and the overall rank order of damage paralleled the viability and immunofluorescence findings (control lowest, followed by the 20-min, 10-min, and continuous groups) (Fig. 5).

DISCUSSION

In this one-to-one *in vitro* simulation of gated breast radiotherapy, prolonging the delivery of a single 2 Gy fraction reduced its tumoricidal efficacy. Rapid, continuous delivery (reproducing conventional tangential treatment) produced the greatest loss of viability and the most DNA double-strand break signal, whereas fragmenting the same dose over 10 or 20 min, as occurs during respiratory gating, was associated with progressively higher viability and fewer residual γH2AX foci. This pattern is consistent with the classical inverse dose-rate effect, in which lower, protracted dose rates allow sublethal damage repair to proceed during irradiation and thereby reduce cytotoxicity.[8,11]

The three independent readouts were mutually concordant. Viability was lowest, immunofluorescence γH2AX foci were highest, and the undamaged (negative) flow-cytometric fraction was smallest after continuous delivery, with the intermittent groups intermediate and the 20-min group closest to control. This internal consistency strengthens the central observation that intrafraction delivery time, independent of total dose, modulates the biological effect on breast cancer cells, and it provides a cellular correlate for the clinical scenario, in which patient non-compliance prolongs the gating window.

Our findings extend a body of radiobiological work on protracted delivery to a breast cancer model. Sterzing et al.[12] reported increased clonogenic survival of TK6 and MeWo cells with dose protraction. Shibamoto et al.[13] observed a 9–14% reduction in biological effect during intermittent exposure of EMT6 and SCCVII cells, estimating that an 8–16% dose increase would be required to compensate. Moiseenko et al.[14] showed that extending delivery time increased survival and decreased residual γH2AX. Wang et al.[15] predicted clinically meaningful reductions in effective dose for fraction times of 15–45 min, particularly for tumors with low α/β and short repair half-times. Keall et al.[16] demonstrated a reproducible survival increase with prolonged gated- and IMRT-type delivery, identifying overall delivery time as the dominant determinant.

Mechanistically, delivering 2 Gy over 10 or 20 min corresponds to mean dose rates of approximately 0.2 and 0.1 Gy/min, within the low-dose-rate range, while

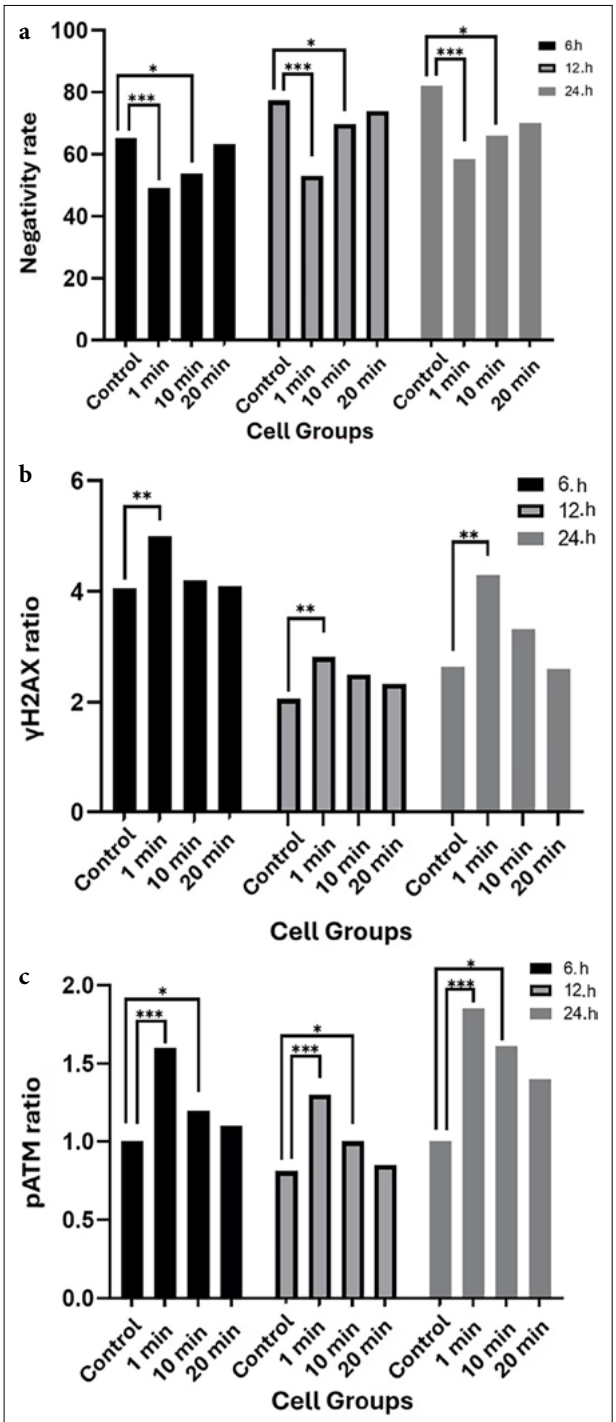


Fig. 5. Flow-cytometric analysis at 6, 12 and 24 h: (a) Negativity (undamaged cells), (b) γH2AX, and (c) phospho-ATM (pATM). The undamaged fraction was lowest after continuous delivery; γH2AX and pATM followed a biphasic course (peak 6 h, nadir 12 h, secondary rise 24 h), with the continuous and 10-min groups elevated above control. Bars show mean±standard deviation.

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the on–off beam pattern of gating further resembles a pulsed low-dose-rate exposure, in which inter-pulse intervals permit partial recovery.[8,11] Lower dose rates have been associated with attenuated accumulation of double-strand breaks and reduced damage signaling over time in both tumor and normal cells,[8–10] providing a plausible basis for the reduced tumoricidal effect seen with longer delivery.

γH2AX and pATM displayed a biphasic time course, peaking at 6 h, declining at 12 h, and rising again at 24 h. The early peak and subsequent decline are consistent with rapid recognition of double-strand breaks followed by effective repair.[17] A secondary rise at 24 h may reflect unrepaired or misrepaired damage, secondary oxidative injury, or progression to apoptosis, during which internucleosomal DNA fragmentation can itself elevate γH2AX.[18] The two methods captured complementary aspects of the response: flow cytometry quantified the total signal across the population, whereas immunofluorescence enumerated discrete nuclear foci, and their combined use provides a more complete picture of damage dynamics.[18] A low level of γH2AX was present in the non-irradiated control, as expected for a transformed cell line with intrinsic genomic instability, and this did not alter the consistent ranking of damage across delivery schedules.

These results have a direct clinical corollary. Respiratory-controlled techniques are adopted specifically to reduce cardiac dose,[3,4,6,7] but they inherently lengthen and fragment beam delivery, and our data suggest that this prolongation may, in turn, attenuate the tumoricidal effect on breast cancer cells. The effect was modest and, in formal testing, reached significance only for the continuous group relative to the non-irradiated control; nonetheless, the consistent trend across three concordant endpoints indicates that intrafraction delivery time is a potentially modifiable parameter. Where clinically feasible, minimizing beam-on time – through patient coaching, stable breath-hold, and efficient gating – may help preserve tumor control while retaining the cardiac benefit and the trade-off may be most relevant in patients who struggle to maintain the gating window.

Limitations of the Study

This study has limitations. It used a single cell line (MCF-7), a single dose (2 Gy), and three delivery durations, with viability and marker-based DNA damage endpoints rather than clonogenic survival; these choices were made to isolate the effect of intrafraction delivery time under clinically relevant conditions. The number of analyzable replicates was limited for some flow-cytometric endpoints, so those comparisons should be regarded as supportive rather than definitive. Statistical testing compared each irradiated group with the non-irradiated control (Dunnett's test); the irradiated groups were not compared directly with one another, so the delivery-time gradient across the viability and DNA-damage endpoints represents a consistent numerical trend across three concordant readouts rather than a formally tested between-group difference. Clonogenic assays, apoptosis markers (e.g., Annexin V and caspase-3), reactive oxygen species measurement, and repair-pathway profiling (e.g., Rad51 and Ku70/80) would further define the underlying mechanisms, and breast cancer subtypes with differing fractionation sensitivity should be examined before clinical extrapolation.[11]

CONCLUSION

Prolonging fraction delivery reduced the tumoricidal efficacy of 2 Gy irradiation in MCF-7 breast cancer cells, with higher viability and fewer residual DNA double-strand breaks as delivery time increased. Because respiratory-controlled techniques inherently extend and fragment beam delivery, intrafraction delivery time merits consideration as a potentially modifiable parameter, and the radiobiological consequences of protracted gated delivery warrant further preclinical and clinical study.

Ethics Committee Approval: Ethics committee approval was not required, as this study was conducted exclusively *in vitro* using a commercially available, established cell line.

Informed Consent: Not applicable.

Conflict of Interest Statement: None declared.

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