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FULL PAPER

4D radiobiological modelling of the interplay effect in conventionally and hypofractionated lung tumour IMRT

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Objective: To study the impact of the interplay between respiration-induced tumour motion and multileaf collimator leaf movements in intensity-modulated radiotherapy (IMRT) as a function of number of fractions, dose rate on population mean tumour control probability ($\overline{\text{TCP}}_{\text{pop}}$) using an in-house developed dose model.

Methods: Delivered dose was accumulated in a voxel-by-voxel basis inclusive of tumour motion over the course of treatment. The effect of interplay on dose and $\overline{\text{TCP}}_{\text{pop}}$ was studied for conventionally and hypofractionated treatments using digital imaging and communications in medicine data sets. Moreover, the effect of dose rate on interplay was also studied for single-fraction treatments. Simulations were repeated several times to obtain $\overline{\text{TCP}}_{\text{pop}}$ for each plan.

Results: The average variation observed in mean dose to the target volumes were $-0.76\% \pm 0.36\%$ for the 20-fraction

treatment and $-0.26\% \pm 0.68\%$ and $-1.05\% \pm 0.98\%$ for the three- and single-fraction treatments, respectively. For the 20-fraction treatment, the drop in $\overline{\text{TCP}}_{\text{pop}}$ was $-1.05\% \pm 0.39\%$, whereas for the three- and single-fraction treatments, it was $-2.80\% \pm 1.68\%$ and $-4.00\% \pm 2.84\%$, respectively. By reducing the dose rate from 600 to 300 MU min^{-1} for the single-fraction treatments, the drop in $\overline{\text{TCP}}_{\text{pop}}$ was reduced by approximately 1.5%.

Conclusion: The effect of interplay on $\overline{\text{TCP}}_{\text{pop}}$ is negligible for conventionally fractionated treatments, whereas considerable drop in $\overline{\text{TCP}}_{\text{pop}}$ is observed for the three- and single-fraction treatments. Reduced dose rate could be used in hypofractionated treatments to reduce the interplay effect.

Advances in knowledge: A novel *in silico* dose model is presented to determine the impact of interplay effect in IMRT treatments on $\overline{\text{TCP}}_{\text{pop}}$.

Respiration-induced organ motion represents a serious challenge regarding the accuracy of dose delivery in radiotherapy (RT) and its impact on clinical outcome. Lung tumours are the most common tumours affected by respiration-induced motion, and local failure (approximately 70% of the cases) is considered as a major cause of tumour-related deaths. Studies have highlighted the importance of dose escalation for improving local control in non-small-cell lung cancers (NSCLC).^{1,2}

Since intensity-modulated RT (IMRT) has the potential to deliver higher doses with fewer normal tissue complications,³ IMRT is often used nowadays to treat lung tumours. Moreover, hypofractionated treatments have been shown to result in better clinical outcomes for medically inoperable early-stage lung tumours.^{4–7} Better targeting accuracy coupled with superior normal tissue sparing and higher dose conformality, especially with smaller treatment fields used in stereotactic treatments, allows clinicians to prescribe extremely high doses in very few fractions (approximately three). With the advent of image-guided RT, this type of

treatment is becoming increasingly common for lung RT. In conventional treatments where the fluence is uniform at the central portion of the fields, respiration-induced tumour motion causes dose blurring at the edges of the target volume, which can be accounted for by a sufficient planning target volume (PTV) margin. However, in multileaf collimator (MLC)-based IMRT delivery where the fluence is non-uniform across the fields, the interplay between respiration-induced tumour motion and the movement of MLC leaves can result in undesired motion artefacts in dose delivery.^{8,9} Consequently, motion management or correction techniques such as tumour tracking or gating have been suggested for treating moving tumours with IMRT.^{10–13} It should also be noted that lung tumours have one of the steepest dose–response curves ($\gamma_{50} = 3.9$),¹⁴ which means that a small change in dose results in a relatively large change in tumour control probability (TCP). Although motion management techniques are currently available, it may not be possible to use such techniques for each patient either owing to time or resource constraints. Thus, it is important to understand and quantify the effect of tumour

motion in IMRT treatments, that is, the interplay effect, in the absence of tumour tracking or gating. By quantifying, we mean not only in terms of absorbed dose, a purely physical quantity, but more importantly in terms of changes in the probability of local tumour control.

Several studies have investigated the effect of respiration-induced tumour motion on IMRT treatments.^{9,15–20} Jiang et al¹⁵ have investigated the effect of interplay for three different modes of IMRT delivery (step-and-shoot with 10 and 20 intensity levels, sliding window) using a 0.6-cm³ farmer chamber positioned at the centre of the artificial tumour in a moving phantom. They found that the mean dose to the moving tumour for all the fields varies from <2% to 3%, but it could be as high as 30% for a single field. They have also shown that the variation in dose is insensitive to the mode of delivery and the dose differences due to interplay decrease as the number of treatment fractions becomes large (approximately 30). This has been previously emphasized by Bortfeld et al⁹ who showed by statistical analysis that the mean dose to a moving tumour is insensitive to the delivery technique, and the standard deviation (SD) in dose for a 30-fraction treatment is generally <1% of the mean dose. However, the conclusion derived from point-dose measurements by Jiang et al does not provide a complete picture of the interplay effect to the overall tumour volume. Using two-dimensional (2D) film measurements, Berbeco et al²¹ have shown that the SD of the dose to a pixel inside the target volume can be as high as 2–4% for single-fraction treatments, which corresponds to stereotactic radiosurgery, although the effect is reduced to 0.4–0.7% with 30 fractions. According to their measurements, the maximum dose in the target varies <1%, while the minimum dose varies up to approximately 6%. This indicates that there could be considerable underdosage of the target volume even for treatments with large number of fractions and the effect of interplay is significant for hypofractionated treatments. In a recent study by Zhao et al²² in a three-fraction treatment, the results showed that the clinical target volume (CTV) could be considerably underdosed owing to the interplay effect in a Cyberknife® treatment (Accuray Inc., Sunnyvale, CA). Furthermore, Seco et al²³ have emphasized that reduced dose errors owing to the interplay effect in many-fraction treatments will not apply to hypofractionated treatments. Nevertheless, the effect of tumour motion and MLC leaves remains a concern for hypofractionated treatments, and this has been emphasized by American Association of Physicists in Medicine report 91.²⁴

Although there are numerous studies addressing the issues of interplay effects in terms of dose variation in the tumour, studies quantifying the clinical significance of these dose variations are much rarer. Use of TCP as a metric would provide a more valuable insight into the true significance of the interplay effect. As mentioned by Niemierko,²⁵ it would be interesting to know the clinical significance of “x” amount of dose error and “y” amount of geometric error rather than mere variation in the dose. Duan et al¹⁸ have performed a TCP analysis using a moving phantom and found the TCP changes to be 2.3% and 4.3% for five- and single-fraction treatments. However, the volume of the target used in their study is fixed (4.5-cm diameter sphere). TCP values could significantly differ with the volume of the target

even for the same prescribed dose with a uniform clonogen density in the CTV, which is the case in this study. Moreover, the TCP values provided were not calculated from a large number of simulations, which raises concern over its applicability for a population of patients.

METHODS AND MATERIALS

In this study, we use digital imaging and communications in medicine (DICOM) patient data sets of six different patients [three-dimensional (3D) CT image, plan information] covering a range of tumour volumes (31–172 cm³) and a four-dimensional dose model that provides 3D voxel-by-voxel dose accumulation in the target volume inclusive of intrafraction organ motion for step-and-shoot IMRT. This dose model takes into account the number of treatment fractions, and parameters relevant for the radiobiological modelling of lung tumours. Although the dose computation algorithm is fairly simple, it is robust enough to simulate the interplay effect in patient geometry. Moreover, the difference in population mean TCP ($\overline{\text{TCP}}_{\text{pop}}$) calculated from large number of simulations for each plan compared with the static tumour with no motion effects is used in this study and provides more statistically reliable TCP values than those obtained with phantom or film measurements with very few numbers of repeated measurements. To obtain the final dose to a particular voxel, the dose computation is performed for each fraction for each beam segment. Inhomogeneity and scatter effects have been ignored to enable the dose computation algorithm to accumulate the dose in each voxel over a fractionated treatment in a reasonable time. The methodology described here is easy to extend to other delivery techniques and could also be extended to account for scatter and for heterogeneous tissue density using more sophisticated dose calculation algorithms such as the one provided by Yang et al.²⁶

A 20-fraction, 3-fraction and an extremely hypofractionated case of 1-fraction treatment were considered for the analysis. Monitor units (MUs) for the single- and 3-fraction treatment were scaled from the 20-fraction plan to give TCP of 50% for a static tumour (within the linear portion of the dose–response curve); that is, with no motion effects taken into account. Although the dose levels used clinically for hypofractionated treatments would result in extremely high TCP values (approximately 100%), a worst-case scenario of 50% TCP (where TCP is more sensitive to dose variations) is assumed in this study. A simulation is the total dose distribution obtained by the accumulation of dose over the course of a fully fractionated treatment for a given patient. Several simulations are performed per patient to calculate $\overline{\text{TCP}}_{\text{pop}}$.

Lung tumour motion simulation

Lung tumours tend to move in an elliptical path²⁷ rather than in a one-dimensional craniocaudal (CC) direction. But for simplicity, a one-dimensional lung motion with a sinusoidal pattern in the CC direction, as performed in several other studies is assumed here. The position of the tumour at time t is given by Equation (1).

$$P(t) = A \sin(\omega t + \phi) \quad (1)$$

where A is the peak deviation from the centre position of the tumour, ω the angular frequency and ϕ is the phase in radians at which breathing starts.

A clockwise delivery is assumed to map the tumour position for each beam and segment. Since breathing is involuntary and uninterrupted while leaves change their position to the next segment or gantry moves to the next beam angle, the time elapsed during these processes is accounted for while calculating the tumour position for each segment for the given beam angle. A gantry speed of 60 s for full rotation and time duration of 1 s between segments is assumed. Even though breathing motion is continuous, dose calculation is performed using a discretized (one or more positions/segment) time-averaged position $P(t)$ using Equation (2). The parameters used for the tumour motion calculation are given in Table 1.

$$\bar{t} = \frac{t_{\text{start}} + t_{\text{end}}}{2} \quad (2)$$

where t_{start} and t_{end} are the start and end time for the given segment. If the segment has a delivery time greater than the period of one respiratory cycle, the segment is split into segments with delivery time equal to the period corresponding to one respiratory cycle. This corresponds to 50 and 25 MU for the 600 and 300 MU min⁻¹ dose rates, respectively.

Digital imaging and communications in medicine radiotherapy plans

In-house developed software is used to read the DICOM objects including CT, RT structures and RT plans. Three step-and-shoot IMRT plans generated using Eclipse's dose-volume optimizer (Varian Medical Systems, Palo Alto, CA) and three using Pinnacle's direct machine parameter optimization (DMPO; Philips Medical Systems, Madison, WI) in a 6-MV Varian 2100C/D with 120 leaf Millennium MLC are used for the analysis. Default number of 10 intensity levels is used for the Eclipse IMRT plans and the default value of 50 maximum number of total segments for the plan was used in Pinnacle's DMPO. The prescription dose was 55 Gy in 20 fractions for all the plans and the dose-volume constraints for the target and the critical structures were set according to the clinical protocols in use at our centre. The PTV margin was 1 cm in all directions, which is sufficient to account for 2-cm peak-to-peak tumour motion in the CC direction. The MLC starting and end positions on the breathing signal is shown in Figure 1 for a beam with 158 MU.

Dose calculation to a moving target

The field and MLC details are defined for zero degree gantry angle in machine co-ordinate system irrespective of the beam angle used in the DICOM RT plan, whereas the RT structures are defined in patient co-ordinate system. The source position, segment and field shapes were first generated for the zero

degree gantry angle in the patient co-ordinate system and then transformed using a 4×4 homogeneous transformation matrix according to their respective gantry, collimator and couch angles (α , β , γ) as shown in Equation (3).

$$\begin{pmatrix} x_t \\ y_t \\ z_t \\ 1 \end{pmatrix} = \begin{pmatrix} \cos(\alpha) & -\sin(\alpha) & 0 & 0 \\ \sin(\alpha) & \cos(\alpha) & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} \times \begin{pmatrix} \cos(\beta) & 0 & -\sin(\beta) & 0 \\ 0 & 1 & 0 & 0 \\ -\sin(\beta) & 0 & \cos(\beta) & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} \times \begin{pmatrix} \cos(\gamma) & -\sin(\gamma) & 0 & 0 \\ \sin(\gamma) & \cos(\gamma) & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} x_0 \\ y_0 \\ z_0 \\ 1 \end{pmatrix} \quad (3)$$

where $\{x_0, y_0, z_0\}$ and $\{x_t, y_t, z_t\}$ are points for zero degree gantry and transformed according to their corresponding collimator, gantry and couch angles (α , β and γ), respectively. Since all the beam objects like jaw, gantry, collimator, MLC rotate about the isocentre and not the image (CT) origin, a translate-rotate-translate approach, where all the beam objects are translated to the origin, rotated and translated back to the isocentre, is used for all transformations. The target structure of interest (CTV) is divided into voxels of $3 \times 3 \times 3$ mm³. Each MLC segment outline (ψ) is generated as mentioned before using the leaf position details in the DICOM RT plan. A sufficiently long ray is traced from the source position through each target voxel and a ray-segment intersection check is performed as depicted in Figure 2a. Depending on whether the ray is inside the segment or not and how close it is to the segment edge, the dose to the target voxel is calculated using Equations (4–8). The distance between the segment edge and ray is calculated at the isocentre plane as shown in Figure 2b. A linear penumbra model is used for the dose calculation. The radiological path length is calculated using Siddon's raytracing algorithm²⁸ assuming uniform water-equivalent density inside the patient external (body) contour. Dose-per-segment method is used so that target voxels can be shifted for each segment to mimic organ motion and the calculated doses in individual voxels are summed for all segments and beams for all fractions. Since the starting phase of breathing for a particular fraction is unpredictable or not the same, a random phase shift is applied to the organ motion calculation for each fraction in the interval $0 \leq \varphi \leq 2\pi$. The resulting dose distribution and the corresponding cumulative and differential dose-volume histograms (DVHs) are shown in Figure 3b, respectively.

$$D(x, y, z) = \sum_{f=1}^f \sum_{i=1}^{n_b} \sum_{j=1}^{n_s} \text{MU}_{i,j} F_{i,j} \quad (4)$$

where n_b and n_s are the number of beams and segments in beam i , and n is the number of treatment fractions. $F_{i,j}$ is the dose correction factor for segment j in beam i . $F_{i,j}$ is calculated using Equation (5), using the tissue-maximum ratio (TMR) values taken from the "Central axis depth dose data for use in radiotherapy departments: report of a BIR/IPSM working party—

Table 1. Parameters used for motion simulation

Parameter	Value
Amplitude	10 mm
Period	5 s
Dose rate	600 MU min ⁻¹
Segment interval	1 s
Gantry speed	0.166 s per degree

Figure 1. Mapping of mean tumour position $P(\bar{t})$ (indicated with a cross marker) for each segment, grey rectangles represent segment intervals. Circle and square markers represent the start and end of segments.

British Journal of Radiology supplement no. 25²⁹ for a 6-MV linac. Since scatter is ignored in our dose model, the output factor is set to unity for all segments. TMR values for corresponding field sizes at a water equivalent depth are used.

$$F_{ij} = \text{TMR}[\text{wed}(x, y, z), \text{ESF}] \times \text{cf} \times \text{SAD factor} \times \text{pf} \quad (5)$$

where ESF is the equivalent field size, cf is the calibration factor of the linac (1 cGy MU^{-1}), pf is the penumbra factor and wed is the water equivalent depth. The SAD factor and the pf are calculated according to Equations (6) and (7), respectively.

$$\text{SAD factor} = \left[\frac{1000}{1000 - (d_{ic} - d)} \right]^2 \quad (6)$$

d_{ic} is the depth of isocentre and d is the water-equivalent depth of the voxel of interest in millimetres.

$$\text{pf} = \begin{cases} 1, & \text{if } \overline{ST} \varepsilon \varphi \text{ and } d_{\text{edge}} \geq 5 \text{ mm} \\ \text{pf}_{\text{in}}, & \text{if } \overline{ST} \varepsilon \varphi \text{ and } d_{\text{edge}} \leq 5 \text{ mm} \\ 0.016, & \text{if } \overline{ST} \notin \varphi \text{ and } d_{\text{edge}} \geq 5 \text{ mm} \\ \text{pf}_{\text{out}}, & \text{if } \overline{ST} \notin \varphi \text{ and } d_{\text{edge}} \leq 5 \text{ mm} \end{cases} \quad (7)$$

$$\text{pf}_{\text{in}} = 1 - \left[\frac{(5.0 - d_{\text{edge}})}{10.0} \right] \quad (8)$$

$$\text{pf}_{\text{out}} = 0.5 - \left(\frac{d_{\text{edge}}}{10.0} \right) \quad (9)$$

where $\overline{ST}$ is the ray vector from source to the target voxel, d_{edge} is the closest distance between the MLC and the target voxel,

Figure 2. Illustration of dose calculation. (a) Ray-segment intersection, where ray vector from source to the target voxel ($\overline{ST}$) contributes to voxel T_1 but not to T_2 . (b) Multileaf collimator (MLC) outline at the isocentre level with points inside (P1) and outside (P2) the segment. d_{edge} is calculated from the closest edge of the segment to the ray.

Figure 3. Dose distribution calculated in a spherical volume of interest (VOI) and their corresponding dose-volume histograms (DVHs) for the clinical target volume (CTV). (a) Dose distribution calculated with the simple beam model in a spherical VOI. (b) Differential (a) and cumulative (b) DVHs calculated for static CTV using the simple beam model (please note the expanded scale in the x-axis).

PF_{in} is the penumbra factor inside and PF_{out} is the penumbra factor outside the MLC edge.

Population tumour control probability calculation

TCP is calculated using Equation (10), and the $\overline{TCP}_{pop}$ is calculated using the enhanced “Marsden” model³⁰ as shown in Equation (11). σ_α is the value of 0.037 Gy^{-1} , which corresponds to NSCLC, $\bar{\alpha}$ value of 0.307 Gy^{-1} and the clonogen density (ρ_{cl}) is set to $1 \times 10^7 \text{ cells cm}^{-3}$.¹⁴ The number of simulations was repeated until the standard error of mean is ≤ 0.2 . The Nassi-Shneiderman diagram of the simulation process is shown in Figure 4.

$$\begin{aligned}
 TCP = & \frac{1}{\sigma_\alpha \sqrt{2\pi}} \\
 & \times \int_0^\infty \left\{ \prod_i \exp \left[-\rho_{clon} V_i \exp \left[-\alpha D_i \left(1 + \frac{\beta}{\alpha} d_i \right) \right] \right] \right\} \\
 & \times \exp \left[\frac{-(\alpha - \bar{\alpha})^2}{2\sigma_\alpha^2} \right] d\alpha
 \end{aligned} \quad (10)$$

where α and β are intrinsic cell radiosensitivities, d and D are the fractional and total doses in the i th dose bin in the differential DVH, ρ_{cl} is the clonogen density and σ_α is the SD of the interpatient radiosensitivity with mean of $\bar{\alpha}$.

Figure 4. Nassi-Shneiderman diagram of the simulation process. DVH, dose-volume histogram; D_{voxel} , the final accumulated dose; PF, penumbra factor; SD, standard deviation; SEM, standard error of mean; sqrt, square root; TCP, tumour control probability.

$$\overline{\text{TCP}}_{\text{pop}} = \frac{1}{n} \sum_{i=1}^n \text{TCP}_i \quad (11)$$

RESULTS AND DISCUSSION

The TCP values for the 20- and 3-fraction treatments are calculated based on the final accumulated dose (D_{voxel}) in each individual voxels over the course of treatment. This assumes that each voxel receives a dose of D_{voxel}/n for each fraction, which is an approximation. In fact, the dose to each voxel for each fraction in the presence of the interplay effect will be different from the mean D_{voxel}/n .³¹ Thus, the biological effect of non-uniform dose is also a concern in the interplay effect where some voxels receive much less dose in a fraction, while some others receive a very high dose in a fraction. However, for a fractionated treatment, Bortfeld *et al*⁹ have shown that the radiobiological differences are negligible for tissues with high α/β ratio and the differences are large only for tissues with lesser α/β ratio. Since tumours have a high α/β ratio (10 Gy) and the treatments are fractionated, the effect of non-uniform dose to voxels on TCP should be negligible. This concern disappears for single-fraction treatments. The spatial variation of dose (accumulated dose) owing to the interplay effect is shown in Figure 5 for one plan used in the study. For comparison, the dose for the single-fraction plan is set equal to the 20-fraction plan. In this case, a significant underdosage can be observed for the single fraction

plan, but this is just for one treatment and could be the opposite for other treatments.

The percentage variation in the population minimum ($\% \overline{D}_{\text{min}}$), maximum ($\% \overline{D}_{\text{max}}$) and mean ($\% \overline{D}_{\text{mean}}$) dose relative to the static tumour is shown in Figure 6. The mean values ($\% \overline{D}_{\text{min}}$), ($\% \overline{D}_{\text{max}}$), ($\% \overline{D}_{\text{mean}}$) are calculated from the mean of the individual plan values. These values are given in Table 2 along with their SDs. The population mean of ($\% \overline{D}_{\text{min}}$), ($\% \overline{D}_{\text{max}}$) and ($\% \overline{D}_{\text{mean}}$) are <1% for the 20- and 3-fraction treatments but larger for the single-fraction treatments. However, the SD of the 3-fraction treatment is considerably more than that of the 20-fraction treatment, which indicates that individual patients will experience larger variations in dose values for a 3-fraction treatment compared with the 20-fraction treatment. The SDs for the single-fraction treatments are even higher than that of the 3- and 20-fraction treatments. This corroborates very well the finding of Seco *et al*,²³ who showed that reduced dose errors in many-fraction treatments will not work for hypofractionated treatments. Although the effect of interplay on dose variations for conventional and hypofractionated treatments provides some understanding on the nature of the interplay effect, it is more useful to know the clinical significance of these dose variations. Obviously for tumours, TCP will be a more meaningful indicator of clinical outcome.

As shown in Figure 7, the variation in TCP for the 20-fraction treatment with interplay effect is almost equal to the TCP value for static tumours. This shows that for treatments with large number of fractions, the dose errors will be small and thus the effect of interplay on TCP is negligible. This is mainly owing to the underdosing and overdosing of the same voxels in different fractions (with many fractions), which leads to the convergence of voxel doses to dose value in the static case. The degree of variation in dose and TCP between patients for a given fractionation differs strongly, which indicates that the effect of interplay is patient and plan dependent. But a large variation can be observed for three- and single-fraction treatments, mostly in the negative direction. It is interesting to note that few patients could gain from the interplay effect as a result of a majority of the voxels being overdosed, thus also increasing the TCP. However, it is impossible to find this small percentage of patients who would benefit from the interplay effect in reality. Although the TCP loss is unacceptably high for single- and 3-fraction treatments, it is within an acceptable limit (approximately 1%) for the 20-fraction treatment. The mean of the population average TCP values calculated for patients ($\overline{\text{TCP}}_{\text{pop}}$) provides a general idea on how the interplay affects $\overline{\text{TCP}}_{\text{pop}}$. The $\overline{\text{TCP}}_{\text{pop}}$ is shown in Figure 8a for six plans for different fractionation along with the mean of all plans. As with the SD of the dose values, the SD of the $\overline{\text{TCP}}_{\text{pop}}$ are also significantly different from the static case for the three- and single-fraction treatments. This indicates that individual patient TCP values will experience large variations in hypofractionated treatments compared with the static tumour case. This can be observed in Figure 8a that for conventional fractionation the effect of interplay on $\overline{\text{TCP}}_{\text{pop}}$ is very marginal or within acceptable limits ($1.05\% \pm 0.39\%$), but for three- and single-fraction treatments, such as radiosurgeries, it is considerably high; namely, $2.82\% \pm 1.68\%$ and $3.95\% \pm 2.84\%$, respectively.

Figure 5. Axial, sagittal and coronal dose comparison on an isocentre plane for 20- and 1-fraction treatments with the static case.

This clearly indicates that motion management methods are inevitable for hypofractionated treatments to avoid significant loss in $\overline{\text{TCP}}_{\text{pop}}$ (although a small percentage of patients would benefit from the interplay effect) for IMRT of lung treatments. In contrast to our findings, Ong et al³² found that for single-fraction RapidArc treatments, the difference in dose compared with the static tumour to the tumour inclusive of the interplay effect is not significantly higher than the static one. However, these findings were based on 2D dose measurements with films in the coronal plane, which will not provide a complete picture of the effect of dose to the tumour including the interplay. While hypofractionated treatments are subject to a lot of variability to delivered dose to a moving tumour, their increased delivery time (owing to higher dose per fraction) means the dose is being delivered over many breathing cycles. Delivery of dose by each segment over multiple breathing cycles would cancel out the dose differences, which in the case of conventionally fractionated treatments takes place across multiple fractions. This effect can

reduce the dose errors to some extent in hypofractionated and single-fraction treatments where higher doses are delivered per fraction. This can be corroborated with the results of 300 and 600 MU min^{-1} simulations, where 300 MU min^{-1} resulted in lesser TCP loss than 600 MU min^{-1} .

The effect of dose rate on $\overline{\text{TCP}}_{\text{pop}}$ owing to interplay is studied for single-fraction treatments (as there is no significant difference for conventional fractionation) with 300 and 600 MU min^{-1} . The results are shown in Figure 8b. From the figure, it is evident that dose delivery over multiple breathing cycles by reducing the dose rate would reduce the interplay effect. On average, the $\overline{\text{TCP}}_{\text{pop}}$ reduction owing to interplay effect was reduced by approximately 1.5% with 300 MU min^{-1} compared with 600 MU min^{-1} . Although this is not a significant reduction for the range of motion assumed in this study, this indicates that reduced dose rate is beneficial for treating moving targets while no motion management techniques are used. As in other studies,

Figure 6. Percentage change in population minimum ($\%D_{\text{min}}$), maximum ($\%D_{\text{max}}$) and mean dose ($\%D_{\text{mean}}$) for 20-, 3- and 1-fraction (Fr) treatments. The values shown are an average of the average (obtained through several runs of simulation for each plan) change in dose values. The error bars represent the mean standard deviations (SD) obtained from individual SDs ($\sqrt{\sigma_1^2 + \dots + \sigma_n^2/n}$).

Table 2. Percentage variation in population minimum (%D_{min}), maximum (%D_{max}) and mean (%D_{mean}) dose relative to the static tumour with standard deviations for different fractions

Fractions	%D _{min}	%D _{max}	%D _{mean}
20	-0.3 ± 0.6	-0.7 ± 0.5	-0.8 ± 0.4
3	-0.6 ± 1.1	-1.0 ± 1.0	-0.3 ± 0.7
1	-2.0 ± 1.4	-0.3 ± 1.1	-1.1 ± 1.0

there are several assumptions made in this study. It should be noted that a real patient's breathing is very different from the sinusoidal assumption. In fact, the breathing may continuously change amplitude and period making it is difficult to model mathematically.³³ Another important point is that lung tumour is surrounded by a tissue of lower density and the density of this spongy tissue may vary continuously during breathing, which could have a significant effect on the dose delivered to the tumour. It is worth mentioning here that cone beam CT images have shown that the tumour volume may decrease when a long fractionation schedule is used, but the amplitude of the tumour motion mainly depends on the amplitude of lung motion. Adaptive planning strategies have been introduced based on tumour volume shrinkage during the course of treatment and to adapt the fields to the tumour volume, and the cumulative effect of interplay in such a scenario is questionable. However, the use of such techniques is highly debatable at present, as the biological uncertainties are much higher than the physical uncertainties in RT. Moreover, the exact knowledge of microscopic disease extension is unknown and shrinking the fields may miss the microscopic disease and decrease chances of controlling the tumour. The ambiguity concerning the linear-quadratic (LQ) model at high dose per fraction has also been debated.^{34,35} As there is no clear consensus on the inappropriateness of the

LQ model at high dose per fractions, the same classic model is used in this study.

Furthermore, the inhomogeneity and scatter corrections are ignored in this study, which would actually influence the results slightly but the trend of the results should remain the same. As mentioned by Duan et al,¹⁸ the random positioning errors during each fraction (isocentre offset, which would give the actual position of a segment relative to the tumour position) should be accounted for in order to study the exact dose delivered to a tumour inclusive of the interplay effect. One of the major limitations of the dose model presented in this article is that it does not account for scatter and tissue heterogeneity, which is dominant in lung RT. However, the results are compared with the dose distribution of the static tumour case computed from the same dose model and hence the differences should be minimal. But the dose model is extensible to account for these effects, and the patient's real breathing can be used instead of a sinusoidal waveform. Moreover, systematic and random errors can be incorporated into the simulation, as the final displacement of target voxels will be the sum of the three vectors namely, systematic, random and CC shifts. This model can also be used for dynamic treatments. The simulation time to obtain $\overline{\text{TCP}}_{\text{pop}}$ with a reasonable standard error can be greatly reduced by calculating the dose for few fractions individually with random phase shifts and adding them randomly to get the final cumulative dose for n fractions.

CONCLUSION

The effect of interplay on $\overline{\text{TCP}}_{\text{pop}}$ in lung IMRT is negligible for treatments delivered over a large number of fractions. However, the $\overline{\text{TCP}}_{\text{pop}}$ is considerably affected for hypofractionated and single-fraction treatments, such as stereotactic body RT and stereotactic radiosurgery. Motion management techniques should therefore be used in order to maintain $\overline{\text{TCP}}_{\text{pop}}$ loss within

Figure 7. Percentage tumour control probability (TCP) change compared with static tumour for 20-, 3- and 1-fraction (Fr) treatments.

Figure 8. Tumour control probability (TCP) loss owing to the interplay effect. (a) Percentage TCP change for 20-, 3- and 1-fraction (Fr) treatments with standard deviation (SD). (b) The effect of dose rate on interplay for a single fraction treatment with SD.

acceptable limits in the latter cases. When no motion management techniques are employed, dose rate could be reduced to decrease the effect of interplay on the target dose.

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