A study on the influence of breathing phases in intensity-modulated radiotherapy of lung tumours using four-dimensional CT

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ABSTRACT. During gated intensity-modulated radiotherapy (IMRT) treatment for patients with inoperable non-small cell lung cancer (NSCLC), the end-expiration (EE) phase of respiratory is more stable, whereas end-inspiration (EI) spares more normal lung tissue. This study compared the relative plan quality based on dosimetric and biological indices of the planning target volume (PTV) and organs at risk (OARs) between EI and EE in gated IMRT. 16 Stage I NSCLC patients, who were scanned by four-dimensional CT, were recruited and re-planned. An IMRT plan of a prescription dose of 60 Gy per respiratory phase was computed using the iPlan treatment planning system. The heart, spinal cord, both lungs and PTV were outlined. The tumour control probability for the PTV and normal tissue complication probability for all OARs in the EE and EI phases were nearly the same; only the normal tissue complication probability of the heart in EE was slightly lower. Conversely, the conformation number of the PTV, V_{20} of the left lung, V_{30} of both lungs, $D_{\max}$ of the heart and spinal cord, V_{10} of the heart and $D_{5\%}$ of the spinal cord were better in EE, whereas D_{mean} of the PTV, V_{20} of the right lung and maximum doses of both lungs were better in EI. No differences reached statistical significance ($p < 0.05$) except $D_{\max}$ of the spinal cord ($p = 0.033$). Overall, there was no expected clinical impact between EI and EE in the study. However, based on the practicality factor, EI is recommended for patients who can perform breath-hold; otherwise, EE is recommended.

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Radiology

Non-small cell lung cancer (NSCLC) [1, 2] accounts for 80% of all lung cancers for which radiotherapy (RT) is the treatment of choice for inoperable cases. However, the survival rate with RT is low. This, in part, is a result of respiratory motion [3], which may cause a planning target volume (PTV) displacement of more than 2.5 cm [4], leading to a geographic miss or unnecessary irradiation of adjacent normal tissues and organs at risk (OARs). This phenomenon involves different sizes and motion of the PTV at different phases of the breathing cycle, and therefore results in different PTV dose coverage [5].

With the development of four-dimensional CT (4D-CT), intensity-modulated radiotherapy (IMRT) and gating, it is possible to achieve better accuracy, precision and clinical outcomes. At present, there are two different philosophies for applying gating phases: during expiration [6] and during inspiration [7, 8]. The former approach advocates that tumour motion is comparatively stable during exhalation, which minimises the respiratory-induced target motion and allows better reproducibility of margin size. Conversely, the latter approach is based on the argument that, during lung inflation, more normal lung tissue can be spared during the irradiation [7]. In this study, a comparison is made between the use of end-inspiration (EI) and end-expiration (EE) gated IMRT

treatment for a set of NSCLC patients using dosimetric and associated biological indicators.

Methods and materials

Subjects

This is a retrospective study of 16 patients with Stage I NSCLC of the left lung treated by IMRT. The 4D-CT data of all subjects were retrieved from the patient database. Subjects were scanned in the supine position, with a 2.5 mm slice thickness across the whole thorax, during uncoached free breathing on a 16-slice CT scanner (GE Healthcare, Waukesha, WI) [9]. The CT data were then transferred to the iPlan Image treatment planning system (Version 3.0; BrainLAB, Feldkirchen, Germany).

Organ delineation

The 4D-CT data sets were separated into 10 bins, whereby each bin corresponded to a different part of the respiratory cycle evenly spaced in time. Thus, the first bin contained data for the first 10% of the cycle following maximum inspiration; the second bin contained data for the second 10%, and so on. Data in the first two bins were combined to define the EI phase, and those in the sixth and seventh bins were combined to define the EE phase, as illustrated in Figure 1. This figure shows a sinusoidal

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curve simplifying an actual respiration pattern, with a slight elongation in the EE region. All delineations of gross tumour volume (GTV) and OARs were conducted by the same investigator. In each phase, the GTVs in both bins were combined with a 5 mm margin to form the clinical target volumes (CTVs). An internal target volume (ITV) was then formed by combining the two CTVs. To account for the set-up error, a 3 mm set-up margin was added to the ITV to form the PTV. The contours of OARs in both bins of a phase were combined to form simple structures to account for the whole excursion volume within a breathing phase.

Treatment plan

An IMRT plan per respiration phase was generated by the iPlan Dose treatment planning system (Version 3.0; BrainLAB, Feldkirchen, Germany). In each plan, an isocentre was assigned at the centre of the PTV with nine equally spaced coplanar beams [10, 11]. For each subject, 95% of the PTV received at least 100% of the prescription dose of 60 Gy ($D_{95} = 60$ Gy).

Plan evaluation using dosimetric parameters

In this study, dosimetric parameters for the OARs included maximum dose ($D_{\max}$), dose received by the highest 5% volume ($D_{5\%}$), and percentage volumes receiving 10 Gy (V_{10}), 20 Gy (V_{20}) and 30 Gy (V_{30}) [11–13]; parameters for the PTV, *i.e.* mean dose (D_{mean}) and conformation number (CN), were used to evaluate the plan quality [14]. The values of CN range between 0 and 1, with 1 being the optimal conformity, and are given by:

$$\text{CN} = \frac{V_{\text{T,pi}}}{V_{\text{T}}} \cdot \frac{V_{\text{T,pi}}}{V_{\text{pi}}} \quad (1)$$

where V_{T} is the total target volume, V_{pi} is the total volume receiving at least the prescription dose, and $V_{\text{T,pi}}$ is the volume within the target receiving at least the prescription dose. The volume definitions are illustrated in Figure 2 [14].

Figure 1. End-expiration (EE) and end-inspiration (EI) phases of a respiratory cycle and the different bins in four-dimensional CT. Information from the 0% and 20% bins form the EI phase, whereas information from the 50% and 70% bins form the EE phase.

Plan evaluation using biological indices

Biological indices, including tumour control probability (TCP) and normal tissue complication probability (NTCP), were used for the evaluation of treatment plans in this study and will be calculated using established models. A statistical model was applied to calculate the TCP [15, 16]. Parameter values are shown in Table 1. The expression for TCP is given by:

$$\text{TCP} = \left(\frac{1}{2} \right) \sum_i v_i \exp \left[2 \gamma_{50} \left(1 - \frac{D_i}{D_{50}} \right) / \ln 2 \right] \quad (2)$$

The Lyman model with equivalent uniform dose was applied for the lungs, with radiation pneumonitis as the end point [15, 17, 18]; the parameters are shown in Table 1. The expression for NTCP is given by:

$$\text{NTCP} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^x \exp(-t^2/2) dt$$

$$\text{where } x = \frac{\text{EUD} - D_{50}}{m \cdot D_{50}} \text{ and } \text{EUD} = \left(\sum_i D_i^{\frac{1}{n}} \frac{V_i}{V_{\text{tot}}} \right)^n, \quad (3)$$

The relative seriality model was applied for the heart and spinal cord, with cardiac mortality and myelitis, respectively, as the end points [12, 19, 20]. The values of these parameters are shown in Table 1. The mathematic expression is represented as:

$$\text{NTCP} = \left[1 - \prod_i (1 - \text{NTCP}(D_i)^s)^{v_i} \right]^{1/s}$$

where

$$\text{NTCP}(D_i) = 2^{-e^{\gamma \left(1 - \frac{D_i}{D_{50}} \right)}} \quad (4)$$

Results

The average volume of the PTVs for the 16 patients in the EI phase was 230 cm³, whereas that in the EE phase

Figure 2. Definition of the volumes used in the conformation number. The solid line is the target volume, V_T ; the dotted line with shaded area is the total volume receiving at least the prescription dose, V_{pi} ; and the hatched area is the volume within the target receiving at least the prescription isodose, $V_{T,pi}$.

was 214 cm³. The average doses to the PTV and OARs among 16 patients in the two respiration phases are shown in Figure 3. The average dose results were very similar between EI and EE phases. Wilcoxon signed rank tests were performed for analysis of the means of dosimetric parameters, and the results are shown in Table 2. The average maximum dose to the spinal cord ($\text{MaxDose}_{\text{SpinalCord}}$) showed significant difference between EE (23.1 ± 9.7 Gy) and EI (24.9 ± 7.9 Gy) ($p=0.033$). Other than this parameter, there were no significant differences for any other comparison. The average maximum doses of the heart, left lung and right lung in EE were 42.8 Gy, 63.2 Gy and 26.5 Gy, respectively, whereas those in EI were 43.7 Gy, 62.5 Gy and 25.9 Gy, respectively. As all PTVs were in the left lung, the right lung did not receive much dose. The average V_{20} of the left lung and right lung in EE was 27.4% and 0.7%, respectively, whereas that in EI was 27.9% and 0.7%, respectively. The average V_{30} of the left lung and right lung in EE was 17.7% and 0.0%, respectively, whereas that in EI was 18.0% and 0.0%, respectively. For the other heart parameter, $V_{10\text{-Heart}}$ in EE was 44.5% and 45.0%. In addition, $D_{5\% \text{ SpinalCord}}$ in EE was 18.3 Gy and 18.9 Gy in EI, respectively. The mean dose to the PTV was the same for the two breathing phases at 60.4 Gy, and was very close to the prescribed dose of 60.0 Gy. The CN was 0.8 and did not show any difference.

Table 3 presents a summary of the biological indices for the plans generated from the two different respiration phases. Differences between EI and EE were very small, and Wilcoxon signed rank test comparisons did not show significant differences ($p>0.05$). The mean and standard deviation of the TCP was $63.7 \pm 0.3\%$ in both phases. The left lung NTCP also showed the same mean and standard deviation of $0.1 \pm 0.2\%$, whereas that of right lung was $0.0 \pm 0.0\%$. Because there was a considerable distance of >2 cm between the PTV and

the spinal cord in most cases, the spinal cord received extremely low doses; in these cases, it was not possible to apply the Wilcoxon's signed rank test. The difference in the mean NTCP of the heart between the two phases was small and did not reach significance.

Discussion

In this study, the PTV dose was optimised and the doses to OARs were minimised owing to the application of IMRT. The drop-off region beyond the prescribed dose in the dose-volume histograms (DVHs) of the PTVs was steep for both breathing phases, leading to an average D_{mean} very close to the prescribed dose. The three subjects with the largest PTVs demonstrated the highest left and right lung doses, and the worst CNs. Apart from these results, there was no obvious relationship between PTV size and other dosimetric results.

Despite the maximum spinal cord doses showing significant differences between the two breathing phases, the spinal cord doses were not expected to cause any clinical impact, as they were well below the 50% complication tolerance dose of 68.6 Gy [12].

The heart NTCP values were close to zero in the majority of treatment plans. However, a few of the NTCPs values were high: subjects 3, 7, 10 and 11 had values of 5.6%, 2.1%, 8.3% and 9.6%, respectively). They shared the common characteristic of having the PTV at the lower lobe of the left lung, close to the heart. This indicated that the heart should be taken into consideration during treatment planning of NSCLC cases, especially those with left-sided tumours.

The left and right lungs were considered separately in this study because the PTV in the left lung was an inclusive criterion. As part of the left lung was in close proximity to the PTV, its dosimetric parameters were much higher than those of the right lung. The V_{20} was a dosimetric parameter used as a radiation pneumonitis indicator. According to Schallenkamp et al [13], 27% of the V_{20} of the left lung in this study would carry a 10–20% probability of developing radiation pneumonitis. However, this was in disagreement with the 1% NTCP result from this study. In fact, many recent studies have modified the Lyman model parameters to achieve the best fit model. With a new set of parameters developed by Rancati et al [21] — $\text{TD}_{50} = 18.4$ Gy, $m = 0.41$ and $n = 0.64$ — the lung NTCP result of this study matches

Table 1. Values of the parameters m , n and D_{50} for normal tissue complication probability (NTCP) calculation for the lungs using the Lyman model and values of the parameters s , γ and D_{50} for NTCP calculation for the spinal cord and heart using the relative seriality model

Organ	m	n	s	γ	D_{50} (Gy)
Lung	0.18	0.87			24.5
Spinal cord			4	1.9	68.6
Heart			1	1.28	52.4

Figure 3. Comparison of sample dose-volume histograms (DVHs) of structures between the end-inspiration (EI) and end-expiration (EE) phases. The white solid line represents the average dose for structures in the EI phase. The black dotted line represents the average dose for structures in the EE phase. PTV, planning target volume.

well with the results of Schallenkamp et al [13]. Nevertheless, the conventional Lyman parameter values were good enough in this study for comparing relative values, such as the comparison between EI and EE.

By considering the differences between dosimetric and biological parameters, it was not possible to make a firm judgement on the optimal gating phase for IMRT treatment, despite the overall results slightly favouring EE (but with no significance). The main reason for this was that all subjects underwent CT scanning in a quiet free-breathing condition. The average lung volume changes from EE to EI for the subjects were within $8\% \pm 5\%$, less than those for the treatment of NSCLC using deep inspiration breath-hold or deep expiration breath-hold. This result concurred with the results of Biancia et al [7], who reported clinically insignificant differences between EE and EI in patients under normal respiration conditions.

From a practical perspective, treatment time can be shortened if a patient is able to collaborate with therapists to carry out breath-holding [7, 22]. The patient carries out 10–13 breath-holds in one fraction, with 12–16 s per breath-hold [23]. Comparing breath-holds between EE and EI phases, Kontrisoova et al [22] reported that most patients found breath-holding during EI less fatiguing than during EE, despite the difference in average treatment time between the two phases being

~10 s. However, in the clinical trial reported by Rosenzweig et al [23], 6 out of 13 patients could not perform the deep inspiration breath-hold technique. Therefore, a breath-hold technique is recommended for IMRT of patients with NSCLC who are in reasonably good health. For patients with breathing difficulties, who are unable to carry out breath-holding, it is advisable to perform irradiation during EE under free breathing for gated IMRT treatment because the PTV movement in EE is relatively slower and more stable than that in EI [7].

Conclusions

There was no difference between the EE and EI gating phases based on the evaluation of biological and dosimetric parameters for NSCLC patients treated under quiet free-breathing conditions. However, when considering the issue of practicality, EI is recommended for patients who can perform breath-holding; otherwise, EE is recommended.

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Table 2. Summary of Wilcoxon signed rank test results of phases and dosimetric indices

	OARs (mean $\pm$ SD)			PTV (mean $\pm$ SD)		
	EI	EE	<i>p</i>	EI	EE	<i>p</i>
<i>D</i> _{mean}				60.4 $\pm$ 0.2	60.4 $\pm$ 0.1	0.495
CN				0.8 $\pm$ 0.1	0.8 $\pm$ 0.1	0.821
MaxDose _{SpinalCord}	24.9 $\pm$ 7.9	23.1 $\pm$ 9.7	0.033			
<i>D</i> _{5%} _{SpinalCord}	18.9 $\pm$ 8.0	18.3 $\pm$ 7.9	0.303			
MaxDose _{Heart}	43.7 $\pm$ 16.2	42.8 $\pm$ 16.3	0.177			
<i>V</i> ₁₀ _{Heart}	45.0 $\pm$ 20.2	44.5 $\pm$ 23.0	0.980			
MaxDose _{L Lung}	62.5 $\pm$ 2.1	63.2 $\pm$ 3.8	0.383			
<i>V</i> ₂₀ _{L Lung}	27.9 $\pm$ 8.1	27.4 $\pm$ 8.0	0.404			
<i>V</i> ₃₀ _{L Lung}	18.0 $\pm$ 5.4	17.7 $\pm$ 5.7	0.376			
MaxDose _{R Lung}	25.9 $\pm$ 11.8	26.6 $\pm$ 14.6	0.305			
<i>V</i> ₂₀ _{R Lung}	0.7 $\pm$ 1.1	0.7 $\pm$ 1.2	0.770			
<i>V</i> ₃₀ _{R Lung}	0.0 $\pm$ 0.1	0.0 $\pm$ 0.1	n/a			

EI, end-inspiration; EE, end-expiration; OAR, organ at risk; PTV, planning target volume; CN, conformation number; SD, standard deviation; L, left; R, right.

Table 3. Summary of Wilcoxon's signed rank test results of phases and biological indices

	NTCP (mean $\pm$ SD)			TCP (mean $\pm$ SD)		
	EI	EE	<i>p</i>	EI	EE	<i>p</i>
PTV				63.7 $\pm$ 0.3%	63.7 $\pm$ 0.3%	0.447
Spinal_cord_union	0.0 $\pm$ 0.0%	0.0 $\pm$ 0.0%	n/a			
Heart_union	1.8 $\pm$ 3.2%	1.7 $\pm$ 3.1%	0.652			
L_lung_union	0.1 $\pm$ 0.2%	0.1 $\pm$ 0.2%	0.447			
R_lung_union	0.0 $\pm$ 0.0%	0.0 $\pm$ 0.0%	0.509			

EI, end-inspiration; EE, end-expiration; NTCP, normal tissue complication probability; TCP, tumour control probability; PTV, planning target volume; n/a, not applicable; SD, standard deviation; L, left; R, right.

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