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Respiratory gaiting

The potential clinical benefit of respiratory gated radiotherapy (RGRT) in non-small cell lung cancer (NSCLC)

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ABSTRACT

Background: There is a great deal of excitement regarding respiratory gated radiotherapy (RGRT), however there remain potential errors and controversies surrounding its use. We aim to predict an improvement in the clinical outcome of RGRT in comparison with that of continuous (non-gated) irradiation by analysing toxicity parameters.

Materials and methods: The 4DCT scans of 15 patients, with node-positive lung cancer and >5 mm of tumour movement, were used for this retrospective analysis. End-inspiration and end-expiration plans were created and the toxicity parameters were compared to continuous (non-gated) 4DCT plans.

Results: Median reduction in V20 with inspiratory gating and expiratory gating, using a 10 mm set-up margin, was 2.0% (range 0.7% to 3.9%) and 0.6% (range −1.1% to 4.7%), respectively. The reduction in MLD was 2.1 Gy (range 0.6 to 3.9 Gy) and 1.6 Gy (range −1.0 to 3.9 Gy), respectively.

Conclusions: Although there is a widespread excitement regarding this technique, this study demonstrates that there is limited reduction in toxicity parameters with the use of RGRT in comparison with continuous (non-gated) 4DCT irradiation. Due to the additional potential errors involved in RGRT, we feel that currently, it should only be performed if comparative planning of RGRT plans and continuous (non-gated) 4DCT plans has been undertaken and a likely clinical benefit has been confirmed.

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The use of four-dimensional CT (4DCT) in lung cancer radiotherapy reduces geographical miss and reduces normal tissue toxicity by individualising the margin from the clinical target volume (CTV) to internal target volume (ITV) [1,2]. The main steps in target definition for 4DCT are as follows: first a composite of the gross tumour in all phases of the respiration cycle is created, gross internal target volume (GITV); then a margin for microscopic disease is added to create the clinical internal target volume (CITV); finally a margin for set-up error is added to create the planned target volume (4D PTV). This 4D_PTV is designed to ensure satisfactory irradiation of the tumour in all positions throughout the respiration cycle. With the introduction of 4DCT, there has been a great deal of interest regarding the possibility of using the 4DCT to plan and deliver respiratory gated radiotherapy (RGRT). This involves treatment delivery at selected phases of the respiratory cycle which can be achieved using different systems. Within our institution, the Varian RPM system (RPM; Varian Medical Systems, Palo Alto, CA) is used. The patient's respiration cycle is monitored continuously by an external surrogate, an infrared marker box placed on the xiphisternum. The movement of the marker box is picked up by a camera and a respiratory trace is seen in the control room. This trace enables the selection of a respiratory phase or "gate" for treatment delivery and the treatment beam is switched on only during this interval.

RGRT has been shown to reduce the size of the PTV when compared to the standard 4D PTV [3]. The theoretical advantages are reduction in toxicity; potential for dose escalation; and fewer patients having radical treatment withheld on account of large volumes or unacceptable toxicity parameters.

Despite the enthusiasm regarding this new technique, it is essential to be aware of the potential disadvantages and the current controversial issues of RGRT. As with all new sophisticated delivery techniques, there are additional potential errors with RGRT [4].

- One source of geometric uncertainty is the poor correlation between internal tumour motion and movement of the external surrogate when using the Varian RPM system [5]. However it is known that with the use of respiratory coaching, the tumour position variation at end-inspiration and end-expiration can be reduced and the reproducibility of the breathing cycle can be improved [6,7]. Spoelstra et al. used static MV images taken during RGRT treatment to calculate the standard deviations of

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systematic ($\sum$) and random (σ) errors in tumour position and found them to be 1.8 and 1.7 mm, respectively [8]. Despite this, unease regarding disparities between external surrogate and internal tumour position remains.

- A further disadvantage of RGRT is that due to irradiation only proceeding during a specific respiratory 'gate' or 'phase', the radiotherapy beam spends around 80% of the respiration cycle switched off. Treatment delivery therefore takes longer which can in turn increase the risk of shifts in patient position [9].
- With the use of a single 4DCT planning scan, for either RGRT or continuous (non-gated) 4DCT treatment, the 4DCT scan captures only a snapshot of respiration-induced tumour motion due to the limited duration of imaging. Systematic errors in the treatment plan and random errors during treatment can occur in both RGRT and continuos (non-gated) 4DCT treatment if what is visualised on the planning 4DCT is not representative of intrafraction motion during treatment [10]. These errors are caused by changes in intrafraction respiration-induced tumour motion [11,12], intrafraction heartbeat-induced tumour motion and tumour hysteresis [13].
- There remains differing ideas regarding whether the selected phase of respiration should lie in end-inspiration or end-expiration [14]. End-inspiration captures the lung at maximum expansion therefore potentially sparing more normal lung tissue [15] however the tumour remains in end-inspiration for significantly less time therefore there is a smaller treatment window [16] and the end-inspiration tumour position is more variable than the end-expiration tumour position. In end-expiration, there is a longer treatment window as the tumour remains in end-expiration for more time, but the lung is compressed therefore more lung is within the treatment field.
- There also remains controversy concerning the threshold of tumour motion where RGRT should be considered. The AAPM recommended respiratory management for tumour movement greater than 5 mm [17], Spoelstra et al. used 7.5 mm, Starkschall et al. tried to prove that tumour motion could be used to predict those patients who would have the most clinical benefit, but they only found a correlation between tumour motion and clinical benefit with RGRT in small tumours (GTV < 100 cm^3, [18]).

In view of these concerns and controversies, it is imperative to quantify the clinical benefit to patients that RGRT provides, when compared to continuous (non-gated) 4DCT treatment. As yet, there are no randomised clinical trials and only one paper suggesting that there is a reduction in lung V20 with RGRT [16]. There is no consensus on which parameters can predict an improvement in clinical outcome when comparing RGRT to continuous irradiation of 4DCT; however the toxicity parameters that are routinely used in clinical practice can be used as surrogates. These include the volume of lung receiving 20 Gy (V20 lung); volume of lung receiving 5 Gy (V5 lung); mean lung dose (MLD); and volume of oesophagus receiving 50 Gy (V50 oes). If the toxicity parameters are reduced with RGRT in comparison with continuous (non-gated) 4DCT treatment, we know that the three theoretical benefits of RGRT could be achieved: toxicity will decrease; there is potential for dose escalation; and more patients would have toxicity parameters within the acceptable levels to proceed to radical radiotherapy.

There were four aims of this study (1) quantify the improvement in clinical outcome of RGRT in comparison with that of continuous (non-gated) 4DCT irradiation, by using toxicity parameters as surrogates for clinical outcome; (2) assess the correlation between tumour motion and benefit of RGRT with a view to identifying a threshold of tumour motion where RGRT should be considered; (3) compare the benefit of inspiration RGRT to expiration RGRT; (4) assess whether the benefit of RGRT is greater when smaller set-up margins (CITV to PTV margin) are used.

Materials and methods

Patient data acquisition

CT image data-sets of consecutive node-positive lung cancer patients were reviewed retrospectively. These patients had previously undergone 4DCT for treatment planning and completed routine radical radiation to a dose of 55 Gy in 20 fractions with continuous (non-gated) 4DCT treatment. In order to select patients for the study, an assessment of tumour motion was undertaken using the cine-movie facility on an Advantage 4D workstation (GE Healthcare, UK). The maximum distance the apex and inferior border of the primary tumour moved during the respiration cycle was measured using the straight line-measuring device. Any patient with >5 mm cranio-caudal tumour movement at either of these points was eligible. Fifteen consecutive patients were selected.

The 4DCT image acquisition has been reported in detail previously [19]. In brief, patients were scanned on a GE Lightspeed RT 16 Multi-slice CT scanner (GE Healthcare, UK) with scanning parameters set at 120 kV, 20 mA with a slice thickness of 2.5 mm. The patients were audio-coached, with the rate of respiration set at their initially recorded respiratory rate. The RPM System is used to record a trace of the patient's respiratory cycle during acquisition of the scan. In each couch position, the scanner acquired 10 consecutive scans over the course of one breathing cycle. These scans were sorted using the Advantage 4D workstation into 10 phase-bins representing the 10 phases of the respiratory cycle.

Delineation of targets

A radiation oncologist delineated three different GITVs for each patient using Varian Eclipse Treatment Planning System, software version 8.6 (Varian Medical Systems, Palo Alto, CA). The different GITVs were created to represent, the full extent of respiratory motion, end-inspiration and end-expiration.

To delineate the GITV for gating in end-expiration, Exp_GITV, the cine-movie of all phase-bins was reviewed. The Exp_GITV was delineated using the phase-bin with the tumour in the most superior position. The Exp_GITV was then reviewed in the surrounding two phase-bins and enlarged to encompass any additional tumour visualised. This additional tumour visualised represents tumour movement during the imaging of the three expiratory "bins". The GITV for gating in end-inspiration, Insp_GITV, was created in the same way however this time identifying the phase-bin with the tumour in the most inferior position and the surrounding two phase-bins. A composite of Exp_GITV and Insp_GITV was created to represent the positional variation of the tumour throughout all phases of respiration (4D_GITV). A margin of 5 mm was added to encompass microscopic invasion to each of these GITVs and then two different planned target volumes (PTV) for each GITV were created using set-up margins of 5 and 10 mm, respectively. This created six different PTVs:

- ***4D_PTV (10 mm margin)*** – 4D_GITV with a 5 mm for microscopic spread and 10 mm set-up margin.
- ***Insp_PTV (10 mm margin)*** – Insp_GITV with a 5 mm for microscopic spread and 10 mm set-up margin.
- ***Exp_PTV (10 mm margin)*** – Exp_GITV with a 5 mm for microscopic spread and 10 mm set-up margin.
- ***4D_PTV (5 mm margin)*** – 4D_GITV with a 5 mm for microscopic spread and 5 mm set-up margin.
- ***Insp_PTV (5 mm margin)*** – Insp_GITV with a 5 mm for microscopic spread and 5 mm set-up margin.
- ***Exp_PTV (5 mm margin)*** – Exp_GITV with a 5 mm for microscopic spread and 5 mm set-up margin.