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4D VMAT, gated VMAT, and 3D VMAT for stereotactic body radiation therapy in lung

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Abstract
Four-dimensional volumetric modulated arc therapy (4D VMAT) is a treatment strategy for lung cancers that aims to exploit relative target and tissue motion to improve organ at risk (OAR) sparing. The algorithm incorporates the entire patient respiratory cycle using 4D CT data into the optimization process. Resulting treatment plans synchronize the delivery of each beam aperture to a specific phase of target motion. Stereotactic body radiation therapy treatment plans for 4D VMAT, gated VMAT, and 3D VMAT were generated on three patients with non-small cell lung cancer. Tumour motion ranged from 1.4–3.4 cm. The dose and fractionation scheme was 48 Gy in four fractions. A B-spline transformation model registered the 4D CT images. 4D dose volume histograms (4D DVH) were calculated from total dose accumulated at the maximum exhalation. For the majority of OARs, gated VMAT achieved the most radiation sparing but treatment times were 77–148% longer than 3D VMAT. 4D VMAT plan qualities were comparable to gated VMAT, but treatment times were only 11–25% longer than 3D VMAT. 4D VMAT’s improvement of healthy tissue sparing can allow for further dose escalation. Future study could potentially adapt 4D VMAT to irregular patient breathing patterns.

(Some figures may appear in colour only in the online journal)

1. Introduction
Stereotactic body radiation therapy (SBRT) in the treatment of lung cancers is growing because its outcomes rival those of surgical resection (Palma et al 2010). A meta-analysis of 34 lung cancer SBRT studies involving 2587 patients reported 3-year local control rates of 87% for tumours measuring greater than 3 cm (Zhang et al 2011a). SBRT delivers 48–60 Gy in fewer
fractions (3–10 fractions) than conventional radiation therapy (60 Gy in 30 fractions). The larger dose/fraction in SBRT can increase unwanted toxicity in adjacent organs at risk (OAR). Centrally located tumours have higher associated toxicity compared to peripherally located lung tumours in three-fraction SBRT (Timmerman et al 2006). This has led to higher fraction SBRT regimes in an attempt to reduce normal tissue toxicity which may reduce the benefit and limit the applicability of SBRT. It is therefore critical to minimize the irradiated volume of healthy tissues while delivering the prescribed dose to the tumour.

The common use of large treatment margins in lung cancer is in direct conflict with SBRT’s requirement of reduced treatment field size. Tumours in the lung tend to move during treatment due to respiratory motion. To account for this, an additional margin for tumour motion is typically added to the gross tumour volume (GTV) when generating the planning target volume (PTV). This strategy can lead to greater volumes of healthy tissue being irradiated (Trofimov et al 2005) as lung motion amplitudes can be as large as 3 cm or more (Keall et al 2006). With the ongoing implementation of more sophisticated imaging techniques that provide greater detailed information on tumour motion and deformation such as 4D CT (Ford et al 2003, Keall et al 2004b, Langner and Keall 2009), 4D cone-beam CT (Sonke et al 2005, Dietrich et al 2006, Li et al 2006), and MRI (Liu et al 2004, Plathow et al 2006, Cervino et al 2011), alternative treatment strategies that minimize motion margins have been developed.

Two strategies that have been shown to reduce the volume of irradiated healthy tissues are respiratory-gated radiation therapy (Shirato et al 2000, Vedam et al 2001, Nicolini et al 2010, Qian et al 2011) and dynamic multi-leaf collimator (DMLC) tracking radiation therapy (Suh et al 2009, Xu et al 2009, Falk et al 2010, Gui et al 2010, Sun et al 2010). Gating minimizes the treatment margin by irradiating the tumour only when it is in a given location, but the inherent duty cycle of 30–50% (Keall et al 2006) markedly extends treatment time. DMLC tracking follows the tumour motion by using the MLC leaves thus potentially allowing for a 100% duty cycle and a more time efficient delivery. However, tracking only alters the shape of the radiation field based on tumour trajectory. Neither the field shape nor its intensity is modified to account for the relative motion between the target and nearby healthy tissues (Suh et al 2009). Previous studies have shown that the changing anatomy of the entire patient can result in superior OAR sparing in certain phases over others (Keall et al 2004a, Trofimov et al 2005, Suh et al 2009). In addition, tracking may have residual dose errors as it cannot fully account for tissue density changes, differential tissue motion along a ray path and tissue motions perpendicular to the leaf motion (McQuaid and Webb 2008). Limitations with tracking are caused by the omission of tissue deformation information at the treatment plan optimization stage. The patient is represented by a static 3D CT image and hence a 3D plan is created. 4D CT data is used post-optimization to propagate the 3D plan to other respiratory phases.

To address these limitations, the temporal information of the patient’s anatomy contained in 4D CT data should be fully exploited by incorporating it into the treatment plan optimization stage. This will be referred to as 4D treatment planning. The term ‘4D treatment planning’ has been associated with several treatment planning strategies including the use of a motion encompassing margin, gating and tracking so long as the 4D CT data was used in some post-optimization capacity either to recalculate the delivered dose or to modify the treatment fields. For clarity, the use of ‘4D treatment planning’ in this study will refer to the instances where 4D CT data was directly integrated into the plan optimization. The enhanced performance in healthy tissue sparing of 4D treatment planning has been investigated for tomotherapy (Zhang et al 2004, 2007), IMRT (Trofimov et al 2005, Papiez et al 2007, McQuaid and Webb 2008, Lee et al 2009, Ma et al 2009, Nohadani et al 2010), radiosurgery (Schlaefer et al 2005), and VMAT (Ma et al 2010, Chin and Otto 2011).
The focus of this study was on 4D treatment planning in VMAT (4D VMAT) as its shorter treatment times are highly desirable for SBRT in lung cancer (Ong et al. 2010, 2012, Holt et al. 2011, Brock et al. 2012). Previous 4D VMAT work by Ma et al. (2010) was a feasibility study limited to one lung and one pancreas case using a digital phantom. In the work by Chin and Otto (2011), the different relative motions between a target and an OAR were explored to identify cases where 4D VMAT planning can be more advantageous than tracked or gated VMAT. These studies neither used 4D CT patient data, nor investigated the additional mechanical constraints and their subsequent impact on treatment time caused by the synchronization of the radiation delivery to the patient’s breathing.

In this study, 4D CT data from three patients with non-small cell lung cancer (NSCLC) were used to generate SBRT treatment plans for 4D VMAT, gated VMAT, and conventional 3D VMAT. The primary goal was to discover, based on equivalent tumour coverage, the maximum potential in healthy tissue sparing of each treatment delivery technique. Delivery times were compared. Finally, exploratory tests of 4D VMAT plan robustness to patient breathing phase irregularities was also performed.

2. Methods

2.1. Patient data

4D CT data for three NSCLC patients was obtained from the VU University Medical Centre in Amsterdam (figure 1). The locations and tumour stages were left lower lobe (LLL) stage IIA for patient A, LLL stage IB for patient B, and right lower lobe (RLL) stage IIA for patient C. Contours of relevant targets and OARs were drawn by a radiation oncologist on the max-exhale phase in Eclipse™ from Varian Medical Systems. The GTV volumes on the max-exhale phase for patients A, B, and C were 83.9, 27.4, and 44.3 cm³, respectively. A B-spline algorithm was used for deformable image registration on the CTs of the nine other respiratory phases to the max-exhale phase (Shackleford et al. 2010). Motion of the target was quantified by the displacement of the GTV’s geometric centre. GTV motion was primarily observed in the cranial caudal (CC) axis and was 1.4 cm (patient A), 1.8 cm (patient B) and 3.4 cm (patient C). Motion of the GTV in the other axes ranged from 0.3 to 0.5 cm.

2.2. The 4D VMAT algorithm

Details of the 4D VMAT algorithm written in Matlab™ have been presented elsewhere (Otto 2008, Chin and Otto 2011). Briefly, the continuous arc rotation of the radiation source...
Figure 2. (a) A schematic showing segmentation of the patient’s respiratory cycle into multiple phases. Colours represent specific CT phases 1 through 6. (b) At the start of treatment plan optimization, the arc is coarsely sampled with few beam apertures. (c) As optimization progresses, more beams are inserted. Numbers represent the order in which beam apertures are introduced into the optimization process. (d) By the end of optimization, the arc is fully sampled and sequentially delivered beams correlate to sequential CT phases. The 4D CT data is sampled multiple times over the arc. Note that (a)–(d) are simplified illustrations. Real plan optimizations used 4D CT data with 10 respiratory phases, 360° arcs, at least 177 beam apertures per arc, and 1–3 arcs.

is approximated by multiple static beam apertures. At the start of optimization, the arc is sampled by only a few evenly spaced beam apertures (e.g. 9–13) and the flexibility to alter the beam weights and MLC leaf positions is high. Eventually, more beam apertures are added to the optimization and the flexibility to change machine parameters decreases until the arc is fully sampled (e.g. 177–289 beams/arc). The addition of new beam apertures always occurs halfway between two existing apertures. While other radiation therapy techniques such as gated VMAT and 3D VMAT rely on a static representation of the patient based on 3D CT data, the key characteristic of the 4D VMAT algorithm is its integration of the patient’s 4D CT data into the optimization process. This is achieved by correlating consecutive beam apertures to consecutive CT phases (figure 2). Only one CT phase is assigned per beam, generating treatment plans with respiratory phase-optimized apertures whose deliveries are synchronized to the patient’s breathing motion. 4D CT data used in this study was divided into ten respiratory phases.

The cost function guiding treatment plan optimization is based on dose-volume constraints as described by Bortfeld (1999). The contributing cost of each constraint is calculated using a quadratic dose difference function multiplied by its priority value. Total cost is the sum of all individual constraint costs. The 4D VMAT software also has 3D VMAT and gated VMAT optimization capabilities.

2.3. Dose calculation

4D VMAT optimization currently uses a pencil beam based dose calculation algorithm (Storchi and Woudstra 1996, Storchi et al 1999) and electronic path length scaling is used
Figure 3. DVHs for VMAT plans created on the max-exhale phase (a) patient A. (b) Patient C. Solid lines are for pencil beam based dose calculations with electronic path length correction. Dashed lines are for rescaled MC based dose calculations.

<table>
<thead>
<tr>
<th>OAR</th>
<th>Constraint (Gy)</th>
<th>OAR</th>
<th>Constraint (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>≤ 30</td>
<td>Spinal cord</td>
<td>≤ 21</td>
</tr>
<tr>
<td>Skin &lt;10 cm³</td>
<td>≤ 28</td>
<td>Spinal cord &lt;0.35 cm³</td>
<td>≤ 16.8</td>
</tr>
<tr>
<td>Heart</td>
<td>≤ 33</td>
<td>Spinal cord &lt;1.2 cm³</td>
<td>≤ 11</td>
</tr>
<tr>
<td>Heart &lt;15 cm³</td>
<td>≤ 28</td>
<td>Bronchus</td>
<td>≤ 33</td>
</tr>
<tr>
<td>Great vessels</td>
<td>≤ 49</td>
<td>Bronchus &lt;4 cm³</td>
<td>≤ 15.6</td>
</tr>
<tr>
<td>Great vessels &lt;10 cm³</td>
<td>≤ 43</td>
<td>Stomach</td>
<td>≤ 27</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>≤ 30</td>
<td>Stomach &lt;10 cm³</td>
<td>≤ 17</td>
</tr>
<tr>
<td>Oesophagus &lt;5 cm³</td>
<td>≤ 18.8</td>
<td>Ribs</td>
<td>≤ 40</td>
</tr>
<tr>
<td>Chest wall &lt;30 cm³</td>
<td>≤ 30</td>
<td>Ribs &lt;1 cm³</td>
<td>≤ 32</td>
</tr>
</tbody>
</table>

Table 1. Sample of SBRT dose constraints used in lung treatment planning (48 Gy in four fractions).

For inhomogeneity corrections. This method is generally not recommended for SBRT lung dose calculations (Benedict et al 2010) as it does not model changes in lateral transport of electrons. However, pencil beams allow for fast plan optimization which is particularly essential for large-scale problems such as 4D VMAT where the number of beams/arc ranges from 177–289. In these cases after plan optimization, a final dose calculation using more accurate techniques is usually performed.

To assess the impact of pencil beam based VMAT optimization on DVHs, 3D VMAT test treatment plans for SBRT prescribed to 48 Gy in four fractions were created on the max-exhale 3D CTs of patients A, B, and C (plan constraints in section 2.4, table 1). Dose distributions were recalculated by 3D VMAT Monte Carlo (MC) using source 20 of DOSXYZnrc code (Lobo and Popescu 2010). As expected, pencil beams overestimated target coverage (Scholz et al 2003, Schuring and Hurkmans 2008). Recalculation with MC found that $D_{95}$ of the PTV was lower than the prescribed value by 13–15% which is within the range found by Schuring and Hurkmans (2008). Minimum dose coverage of the GTV could be recovered if the plan MUs were increased by 8.7% for patient A, 7.6% for patient B, and 10.0% for patient C. Examples with the largest dose differences for the pencil beam derived DVHs versus the rescaled MC DVHs are displayed in figure 3. The rescaled MC DVHs show slightly higher dose to the OARs, but otherwise closely followed the form of the pencil beam DVHs.
The main goal of this study was to compare the relative performance of 4D VMAT, gated VMAT, and 3D VMAT in sparing of OARs. The results that will be subsequently presented are not invalidated due to the use of pencil beams in the plan optimization as figure 3 demonstrates that only small shifts in the rescaled MC DVH curves occurred. These shifts will affect all techniques equally. It is inferred that the close agreement in DVH form between pencil beam and rescaled MC will carry over to 4D dose calculations. Work on a 4D VMAT MC dose calculation algorithm using 4D CTs is pending.

The reported MUs and treatment times in this study should be viewed from a perspective of relative comparison between the tested treatment techniques. These values will inevitably change once faster and more accurate dose calculation algorithms for plan optimization are employed (Gu et al 2011, Jia et al 2011, Peng et al 2012) along with the higher dose rates used in flattening filter free beams (Ong et al 2012).

2.4. Treatment planning process

As mentioned in section 2.2, 4D VMAT incorporates all ten 4D CT phases into the optimization. For both gated VMAT and 3D VMAT, the 3D treatment planning CT and structures were created by merging and averaging the CTs from the relevant phases of the 4D CT data to create an average 3D CT (gated VMAT: 4–6 phases, 3D VMAT: 10 phases). All 4D CT image processing, registration and deformation were performed using the Plastimatch software (http://plastimatch.org/). For gated VMAT, the gating window was set by constraining residual tumour motion to 3 mm or less resulting in duty cycles of 40% for patient A, 60% for patient B, and 50% for patient C. The max-exhale phase was always within the gating window. Gating at phases closer to max-inhale was not selected because for the chosen gating window, duty cycles would have been 20% for patient A and 10% for patients B and C.

Following the SBRT lung protocol at our centre, an experienced treatment planner created VMAT SBRT treatment plans for all three patients on the max-exhale phase with instructions to maximize OAR sparing. SBRT schedule was 48 Gy in four fractions with a minimum of 95% of the PTV volume receiving the prescribed dose. No margin was added to the GTV to create the CTV. The PTV was created by a 5 mm isotropic expansion around the GTV. Table 1 gives a sampling of some of the protocol’s dose constraints. All constraints were strict constraints except for the ribs and chest wall. Exceeding any strict constraint rendered the plan clinically unacceptable. Plans were exported from Eclipse and into the 4D VMAT software. The treatment planner’s optimized dose volume constraints on the max-exhale phase were used as starting points for the 4D VMAT, gated VMAT, and 3D VMAT optimizations of this study.

All results from the treatment plan optimizations were evaluated using a 4D dose volume histogram (4D DVH). 4D DVHs were generated by calculating dose on each phase of the 4D CT image set and then summing the doses onto the reference max-exhale phase using the deformable transformation matrix (section 2.1). For 4D VMAT, calculation of 4D DVHs occurs naturally since delivery of beam apertures are synchronized to specific patient respiratory phases and hence can occur within treatment plan optimization. For gated VMAT and 3D VMAT, where the exact correlation between beam aperture delivery and tumour position is unknown and plan optimization uses 3D CTs, the 4D DVH calculation must be performed post-optimization. When optimization was completed, the entire treatment plan dose was individually calculated on each relevant CT phase (gated VMAT: 4–6 phases, 3D VMAT: 10 phases), summed onto the reference CT, and then averaged by the number of CTs.

To ensure that the 4D DVH comparison between 4D VMAT, gated VMAT, and 3D VMAT was fair, care was required in specifying the target coverage used during plan optimization.
Uniformly requiring all techniques to achieve a 95% coverage of the PTV volume \( (D_{95}) \) by the prescribed dose would have unfairly biased the results of one treatment over another because the PTVs were defined differently in each technique. In 3D VMAT and gated VMAT, an internal target volume (ITV) was formed from merging the GTVs of the applicable CT phases. Expanding the ITV by a 5 mm margin created the merged PTV. For 4D VMAT, there were multiple individual PTVs. The reference PTV was created from a 5 mm expansion around the max-exhale GTV. The PTVs on the other phases were found by deforming the reference max-exhale PTV with the transformation matrix.

The problem with using the merged PTV of 3D VMAT is that multiple studies have already demonstrated that the ITV concept for motion compensation results in a higher than expected dose to the 4D GTV. In other words, margins were larger than needed leading to unnecessary irradiation of greater volumes (Baker et al 2011, Guckenberger et al 2011). Our own preliminary 3D VMAT test simulations using similar clinical margins also confirmed these findings. Figure 4(a) shows an example of an increase in the minimum GTV dose (+2.6 Gy) when the 3D VMAT plan was recalculated using 4D methods. Regarding 4D VMAT PTVs, as the patient cycles from exhale to inhale, tumour and lung volumes can expand in an anisotropic fashion. Consequently, the transformation matrix’s deformation of the 5 mm margin used to define the reference PTV on max-exhale would likely create larger margins at phases closer to max-inhale resulting in an over estimation of PTV sizes at those phases.

The gated VMAT’s merged PTV was less likely to exhibit the problems of 3D VMAT’s merged PTV to the same magnitude because our gating window minimized target motion. Therefore, for the purposes of a comparative study, gated VMAT’s target coverage was chosen as the common plan objective for all three treatment techniques. Prescription was 48 Gy in four fractions with at least 95% of the gated merged PTV receiving the prescribed dose. After a clinically acceptable gated plan was created on gated VMAT’s 3D CT, a 4D dose calculation using 4D CTs was performed post-optimization onto the max-exhale phase as described previously. The gated 4D results for the minimum GTV dose and percentage of the PTV receiving 48 Gy on the max-exhale phase then had to be achieved in the 4D VMAT and 3D VMAT plan optimizations. This was straightforward to accomplish in 4D VMAT because
4D dose calculation on the max-exhale phase occurs within the optimization. However, 3D VMAT, like gated VMAT, optimized on 3D CT data and required a post-optimization 4D dose calculation on 4D CTs. Target coverage of 3D VMAT’s merged PTV was never used as a plan objective.

Only by matching the 4D calculated max-exhale target coverage for all treatment techniques could an unbiased comparison be made of the OAR sparing results. Figure 4(b) shows an example of the OAR dose differences that can occur in 3D VMAT plans if the issue of target coverage is not carefully handled. Greater emphasis was placed on maintaining the max-exhale’s minimum GTV dose with values for all three treatment techniques required to fall within a 0.5 Gy range. For the percentage of the max-exhale PTV covered by 48 Gy, the range in values was within a few per cent (90–94%). This latter criterion had greater flexibility as it was more challenging to control dose fall off without compromising minimum GTV dose due to the disparate nature in technique delivery. Specifically, gated VMAT’s irradiation of the tumour only in a set position resulted in lower 4D calculated max-exhale PTV coverage (90–91%). In contrast, 4D VMAT and 3D VMAT’s irradiation of the tumour along its entire trajectory led to a greater spread in deposited dose and thus slightly greater max-exhale PTV coverage (92–94%).

To ensure that the OAR sparing was maximized for each treatment technique, the creation of treatment plans for 4D VMAT, gated VMAT, and 3D VMAT required an iterative process. As OAR sparing was improved in one technique, treatment plans were re-optimized with stricter dose volume constraints for other techniques in an attempt to match the improvement. Target coverage was maintained and all plans met the strict constraints in table 1. For all three techniques in this section, a single arc of 177 beam apertures was used. Maximum dose rate was 600 MU min⁻¹.

2.5. CT phase bias in 4D VMAT optimization

As treatment plan optimization progresses, the 4D VMAT algorithm gradually adds more beam apertures exactly in between existing beams (section 2.2). A consequence of this design is that during a given step of the optimization, the CT phases are not equally represented. Figure 2 gives a simplified illustration of this problem. From figure 2(b) to (c), plan optimization occurs on the odd numbered CT phases (red, yellow and blue). The even numbered CT phases (orange, green and purple) are not included until figure 2(d). For 4D VMAT simulations in section 2.4 with 10 CT phases and 177 beam apertures, the result was that the first half of the optimization (89 beams) involved odd numbered CT phases and the next 88 beams inserted into the optimization related to even numbered CT phases.

To test whether this phase bias affected the 4D DVH results, 4D VMAT optimizations from section 2.4 were repeated with two different setups. In the first setup, if the original plan started with odd numbered CTs, then the new optimization started with even numbered CTs or vice versa. This setup was called the reciprocal bias setup. In the second setup, the order of beam aperture introduction was altered slightly. Instead of choosing to add a beam that was precisely between two existing ones, the beam immediately adjacent to original insertion point (∼ 2° shift) was chosen in such a fashion that CTs from all phases were more evenly represented throughout the entire optimization (figure 5). This was known as the balanced setup.

2.6. 4D VMAT treatment delivery time

In section 2.4, gated VMAT, 4D VMAT, and 3D VMAT all used the same optimization constraint for the relative change in MUs allowed between beam apertures. However,
4D VMAT requires an extra MU optimization constraint that limits the absolute number of MUs/beam (\(\text{MU}_{\text{beam,max}}\)). This is explained as follows. In its current implementation, synchronization of each beam aperture’s radiation delivery to a patient respiratory CT phase results in a constant gantry rotation speed (Zhang et al 2007, Ma et al 2010). The total treatment time, \(T\), is:

\[
T = N_{\text{arc}} \times N_{\text{beams}} \times t_{\text{phase}},
\]

where \(N_{\text{arc}}\) is the number of identical arcs in the treatment, \(N_{\text{beams}}\) is the number of beam apertures in one arc, and \(t_{\text{phase}}\) is the duration of one respiratory CT phase (figure 2(a)). The 4D VMAT algorithm has the ability to optimize for multiple unique arcs, but this study was restricted to identical arcs due to limits on computational memory.

As \(t_{\text{phase}}\) also represents the time allowed per beam, this subsequently imposes a restriction on the maximum deliverable MU per beam, \(\text{MU}_{\text{beam,max}}\):

\[
\text{MU}_{\text{beam,max}} = t_{\text{phase}} \times \text{MU}_{\text{max}} \times N_{\text{arc}} \times N_{\text{fx}}.
\]

\(\text{MU}_{\text{max}}\) is the maximum dose rate (600 MU min\(^{-1}\)) and \(N_{\text{fx}}\) is the number of treatment fractions.

To maximize its ability to spare healthy tissues, 4D VMAT optimizations in section 2.4 did not include the \(\text{MU}_{\text{beam,max}}\) constraint. Consequently, resulting treatment plan delivery times were three times that of 3D VMAT as a greater number of arcs were inefficiently required to deliver the full MU of a few heavily weighted beam apertures. 3D VMAT and gated VMAT are not subject to this constraint as their deliveries allow gantry rotation speed to accelerate or decelerate depending on beam MUs.

4D VMAT optimizations from section 2.4 were repeated with the \(\text{MU}_{\text{beam,max}}\) constraint and the new 4D DVHs were compared against the original 4D DVHs to determine whether the decrease in optimization flexibility degraded plan quality. The breathing periods tested were 3 and 6 s as this covers the commonly reported respiratory range (Seppenwoolde et al 2002, Suh et al 2008a). Determination of optimization parameters began with setting the 4D VMAT treatment time, \(T\). Lookup tables generated using (1) contained \(T\) values for all valid combinations of \(N_{\text{beams}}, N_{\text{arcs}}\) and \(t_{\text{phase}}\). Values for \(N_{\text{beams}}\) and \(N_{\text{arcs}}\) were chosen such that the \(T\) value was close to the corresponding 3D VMAT treatment plan time while minimizing computational memory. To compensate for the negative effect of the \(\text{MU}_{\text{beam,max}}\) constraint on optimization flexibility, the value of \(N_{\text{beams}}\) can be increased, but at the cost of increased treatment time. Final optimization parameters are shown in table 2.
Table 2. 4D VMAT optimization parameters for treatment of NSCLC patients with SBRT prescription of 48 Gy in four fractions. 4D CT data was divided into ten respiratory phases.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patient</th>
<th>Respiratory period (s)</th>
<th>$t_{\text{phase}}$ (s)</th>
<th>$T$ (min)</th>
<th>$N_{\text{beams}}$</th>
<th>$N_{\text{arc}}$</th>
<th>MU$_{\text{beam_max}}$</th>
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<tbody>
<tr>
<td>A</td>
<td>3</td>
<td>0.3</td>
<td>3.86</td>
<td>257</td>
<td>3</td>
<td>36</td>
<td></td>
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<tr>
<td></td>
<td>6</td>
<td>0.6</td>
<td>3.86</td>
<td>193</td>
<td>2</td>
<td>48</td>
<td></td>
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<tr>
<td>B &amp; C</td>
<td>3</td>
<td>0.3</td>
<td>4.34</td>
<td>289</td>
<td>3</td>
<td>36</td>
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<td></td>
<td>6</td>
<td>0.6</td>
<td>4.18</td>
<td>209</td>
<td>2</td>
<td>48</td>
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</table>

Table 3. Factors that affect the length of time random delivery errors can occur before being detected and corrected by an on-line imaging system.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Respiratory period (s)</th>
<th>$t_{\text{phase}}$ (s)</th>
<th>System response time (s)</th>
<th>System response time (phases)</th>
<th>Period for undetected errors (phases)</th>
<th>No of consecutive incorrectly delivered beams</th>
<th>Period of one incorrect delivery (s)</th>
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<tr>
<td>A &amp; C</td>
<td>3</td>
<td>0.3</td>
<td>0.6</td>
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<td>2</td>
<td>4</td>
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<td>1</td>
<td>2</td>
<td>3</td>
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</tr>
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<td>0.6</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>0.6</td>
<td>0.6</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>2.4</td>
</tr>
</tbody>
</table>

2.7. Robustness of 4D VMAT delivery to desynchronization

4D VMAT is a respiratory correlated technique. In other words, treatment plans are tailored to specific patient respiratory motions given by 4D CT data. Thus, during treatment delivery, the patient must breathe in a similar fashion as during planning 4D CT. Unfortunately, respiratory motion of free-breathing patients can show variability from cycle to cycle (George et al 2005, Suh et al 2008a), which could degrade the final 4D VMAT DVH. Tumour motion would need to be modelled to achieve a regular and reproducible respiratory pattern (Low et al 2005, McClelland et al 2006) and audiovisual respiratory guidance would be required during the radiation delivery (George et al 2005, Venkat et al 2008). Monitoring of tumour location throughout treatment would require a real-time imaging system (Fallone et al 2007, Liu et al 2008) and a motion prediction algorithm would need to be incorporated to compensate for latency in the radiation delivery system’s response time (Ren et al 2007, Riaz et al 2009).

Despite methods used to regulate and predict patient breathing, desynchronization delivery errors can still occur. To assess the robustness of 4D VMAT to these errors, the plans created in section 2.6 were tested for both systematic and random desynchronization delivery errors. For systematic desynchronization error, two different simulations were performed. The delivery of all beam apertures was offset from their correlated respiratory phases by either a lag or an advance of two phases. This offset size was deemed to be sufficiently challenging to plan quality and any shift greater than this was expected to be detected by an online imaging system.

For random desynchronization error, it was assumed that when patient breathing irregularity occurs, it is unavoidable for beam apertures to be delivered to the incorrect respiratory phases for short segments of time due to: (1) imaging frequency of the real-time imaging system, (2) processing time of the tumour motion prediction algorithm, (3) hardware response time, and (4) undetectable phase shifts in the respiratory pattern due to lack of tumour motion at certain phases (e.g. near exhale). For factors (1) to (3), a total system response time of 0.6 s (table 3, columns 4 and 5) was assumed based on a range of values given in literature (Ren et al 2007, Riaz et al 2009, Cervino et al 2011). In regards to (4), the phase to phase
tumour centroid displacement was examined for each patient. Based on a desynchronization delivery error of two phases, the number of phases where such an offset would alter the tumour’s position by less than 2 mm (table 3, column 6) was determined. The ability to track tumour motion typically has an uncertainty of 2 mm or better (Shirato et al 2000, Cho et al 2008, Liu et al 2008). The total period of consecutive desynchronized beam aperture delivery was conservatively estimated to be the sum of all four listed factors (table 3, column 7 and 8).

To assess 4D VMAT’s robustness to random desynchronization delivery errors, short periods of incorrect delivery calculated in table 3 were randomly introduced throughout the treatment arc. The direction (lag or advance) of each error period’s two-phase offset was also randomized. The more periods of delivery errors that could be inserted into the plan without negatively impacting plan quality, the greater the robustness to desynchronization. For the sake of simplicity, plan quality was defined as maintained if neither the minimum dose to the GTV decreased by more than 1 Gy, nor the maximum dose to any OAR increased by more than 1 Gy. Gauging desynchronization robustness was, therefore, an iterative simulation process with more and more delivery errors inserted until plan quality could no longer be maintained. For a given number of delivery errors, plan quality was considered unaffected if the above limits for its maintenance could not be breached for three repeated simulations. Conversely, only one simulation violating the limits was required to conclude plan quality had degraded.

3. Results

3.1. 4D VMAT, gated VMAT, and 3D VMAT treatment plan comparison

Figures 6 to 8 display the 4D DVH results comparing 4D VMAT, gated VMAT, and 3D VMAT for patients A, B, and C. If evaluation is based solely on the constraints listed in table 1, gated VMAT plans had the better OAR sparing overall, although 4D VMAT’s sparing of a few OARs, such as the heart in patient A (figure 6) and the spinal cord in patient B (figure 7) was slightly superior. Doses to the ribs and chest wall were always greater than the desired constraints due to their overlap with the target. Considering the difference in the range of tumour motions treated by 4D VMAT (1.4–3.4 cm) versus gated VMAT (0.3 cm), the treatment plan qualities between the two techniques were not widely dissimilar with the majority of differences in
mean OAR dose remaining below 0.5 Gy. 3D VMAT had the poorest plan qualities for all patients. The differences in mean OAR doses between 3D VMAT and gated VMAT in many cases were at least 1 Gy and was as large as 3.5 Gy for the liver in patient C (figure 8).

For patient A, none of the OARs with strict constraints were in the immediate vicinity of the tumour; thus, all the treatment plans easily met the requirements of table 1 (figure 6). While 3D VMAT would have a higher probability of chest wall pain and rib fracture, an SBRT fractionation schedule with a higher biological effective dose (BED) could be considered for all three techniques. In the 3D VMAT treatment plan for patient B (figure 7), the strict constraints on the spinal cord and bronchi were barely achieved. Thus, dose escalation with 3D VMAT would be much harder to achieve than with 4D VMAT or gated VMAT. In addition, an extra 16.2–22.4 cm³ of chest wall was exposed to doses above 30 Gy in 3D VMAT versus 4D VMAT and gated VMAT. Similarly for patient C (figure 8), dose escalation using the 3D VMAT delivery would entail a higher risk of complications than 4D VMAT or gated VMAT due to radiation exposure of the oesophagus, ribs and chest wall.
Table 4 contains the values of $V_{5}$, $V_{20}$, and mean lung dose for all three patients. In general, gated VMAT tended to have the lowest values followed by 4D VMAT and then 3D VMAT. VMAT produces plans with highly conformal dose distributions and, therefore, for all three techniques the values for $V_{5}$ and $V_{20}$ were within a few per cent of each other and mean lung dose differences were below 1 Gy. The exception was patient B where the differences between gated VMAT and 3D VMAT were 10.2% for $V_{5}$ and 1.8 Gy for mean lung dose. This was likely due to a combination of two factors: (1) patient B had the smallest GTV volume (27.4 cm$^3$) yet a fairly large tumour displacement (1.8 cm), and (2) the GTV in patient B was surrounded by lung tissue whereas in patient A and C, lung tissue was above the GTV and the diaphragm was immediately below.

Table 4 also contains the per cent plan MUs of gated VMAT and 4D VMAT relative to 3D VMAT. The 3D VMAT plans required 7548 MUs for patient A, 9063 MUs for patient B, and 8189 MUs for patient C. The number of MUs were inversely related to the volume of the GTVs. Gated VMAT and 4D VMAT plans required more MUs than 3D VMAT because beam aperture sizes were smaller. The exception was for patient A with gated VMAT where 1.0% fewer MUs was required, but this is within MU variability during plan generation. 4D VMAT also required more MUs than gated VMAT and 3D VMAT because to better shape dose distribution around the moving target, more complex fluence modulation was necessary. Figure 9 shows an example of 4D VMAT treatment apertures for patient B.
Figure 10. 4D DVH for patient C (motion 3.4 cm). Solid lines are the original 4D VMAT results from section 3.1. Dashed lines are for the reciprocal biased setup (a) or the balanced setup (b).

Table 5. Treatment times for 3D VMAT, 4D VMAT, and gated VMAT to deliver a 12 Gy fraction. Note that 3D VMAT and gated VMAT treatment times are not dependent on the patient’s respiratory period.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Respiratory period (s)</th>
<th>Treatment time (min)</th>
<th>Gated beam interruptions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3D VMAT</td>
<td>4D VMAT</td>
<td>Gated VMAT a</td>
</tr>
<tr>
<td>A</td>
<td>3</td>
<td>3.17</td>
<td>3.86</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>3.86</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>3</td>
<td>3.78</td>
<td>4.34</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td></td>
<td>4.18</td>
</tr>
<tr>
<td>C</td>
<td>3</td>
<td>3.47</td>
<td>4.34</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>4.18</td>
<td></td>
</tr>
</tbody>
</table>

a Treatment times for 4D VMAT assumed reproducible tumour motion.

b Treatment times for gated VMAT only accounted for the duty cycle. Temporal consequences of beam interruptions on gantry rotation were ignored.

3.2. CT phase bias in 4D VMAT optimization

CT phase bias in the 4D VMAT optimization did not have a major affect on treatment plan quality. For both the reciprocal biased and the balanced setups tested and across all three patients, the largest decrease in minimum GTV dose was less than 0.7 Gy and the greatest increase in mean OAR dose was 0.4 Gy. For the investigation of phase bias, dose volume constraints were not altered from those used in section 3.1, but they would only have required minor adjustments to maintain the original minimum GTV dose. Figure 10 shows the 4D DVH results for patient C whose 4D CT had the largest tumour motion (3.4 cm) and thus, was most likely to be affected by the CT bias. There was no major difference between the 4D DVH curves of the original simulation (section 3.1, solid line) and those of the altered setup (dashed lines). In fact, the small observable differences did not favour one setup over another.

3.3. 4D VMAT treatment delivery time

Table 5 displays the calculated estimates of treatment delivery times for 3D VMAT, 4D VMAT, and gated VMAT. The fastest plan deliveries were for 3D VMAT (3.17–3.78 min) followed
closely by 4D VMAT (3.86–4.34 min). Gated VMAT had the longest treatment times (6.68–7.85 min). The treatment times for gated VMAT were calculated based on the duty cycles of 40% for patient A, 60% for patient B, and 50% for patient C. However, in actual clinical delivery of gated VMAT, beam interruptions involve the gantry slowing down to a complete stop followed by a reversal of the gantry rotation until it reaches a position just before the gate-close signal was triggered. This could further increase gated VMAT treatment times from a few per cent to 25% and is highly dependent on the patient respiratory pattern (Qian et al 2011).

4D VMAT treatment delivery times were longer than those for 3D VMAT for two reasons. First, as explained in section 3.1, the total plan MUs for 4D VMAT were always greater than 3D VMAT. Second, to compensate for the reduced optimization flexibility caused by the MUbeam_max constraint (2), the number of beams in an arc (Nbeams) were increased which resulted in longer treatment times (1). To avoid greatly extending treatment times, the values for Nbeams chosen in this study did not fully offset the negative effects of MUbeam_max and therefore, there was some minor degradation in plan quality. Figure 11 compares the 4D DVHs of the 4D VMAT treatment plan optimizations with (dashed lines, section 3.3) and without (solid lines, section 3.1) the MUbeam_max constraint for patient C. Patient C had the largest tumour motion (3.4 cm) and the greatest degradation in plan quality. The MUbeam_max constrained plans were all clinically acceptable and the largest increase in mean OAR dose was limited to 0.5 Gy.

3.4. Robustness of 4D VMAT delivery to desynchronization

Figure 12 displays examples of the effects of systematic and random 4D VMAT treatment desynchronization delivery errors on 4D DVH curves. The solid lines are the original error-free delivered plans from section 3.3 optimized with MUbeam_max while the dashed lines represent the same plans compromised by delivery errors. For the systematic error, the greatest degradation in plan quality occurred for patient B where the respiratory pattern lagged the beam aperture delivery by two phases (figure 12(a)). Only a few OARs are shown for better clarity. The primary impact of the systematic desynchronization error was the loss of GTV

![Figure 11. 4D DVH for patient C (motion 3.4 cm). Solid lines are the original 4D VMAT results from section 3.1. Dashed lines are for treatment plan optimizations using the MUbeam_max constraint for a patient respiratory period of 3 s (a) and 6 s (b).](image-url)
Figure 12. (a) Example of 4D VMAT DVH for systematic error: patient B, respiratory period 3 s and patient breathing lagging behind treatment delivery by two respiratory phases for the entire treatment. (b) Example of 4D VMAT DVH affected by random error: patient A, respiratory period 6 s and 15% of beams delivered incorrectly to patient breathing by a lag or advance of two respiratory phases. Solid lines represent the original error-free delivery and dashed lines represent the error-prone delivery.

Table 6. Robustness of 4D VMAT to random treatment delivery errors. Beam aperture deliveries were randomly desynchronized from their intended respiratory phases.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Respiratory period (s)</th>
<th>Period of one incorrect delivery (s)</th>
<th>Total% of allowed incorrectly delivered beams</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>3</td>
<td>1.2</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>1.8</td>
<td>15%</td>
</tr>
<tr>
<td>B</td>
<td>3</td>
<td>1.5</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>2.4</td>
<td>10%</td>
</tr>
<tr>
<td>C</td>
<td>3</td>
<td>1.2</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>1.8</td>
<td>10%</td>
</tr>
</tbody>
</table>

coverage. For all simulations tested, minimum GTV dose decreased anywhere from 2.0 to 5.5 Gy. Overall impact on the OARs was negligible. Increases in mean OAR doses remained below 0.1 Gy. There was potential for some OARs, such as the bronchi, to see an increase in their maximum dose by several Gy but under our current SBRT protocol, no strict constraints ever came close to being violated.

Figure 12(b) shows an example of a 4D DVH curve affected by random treatment desynchronization delivery errors for patient A with respiratory period of 6 s. The minimum GTV dose decreased by 0.9 Gy while the bronchi had the greatest increase in maximum dose at 0.9 Gy. Table 6 summarizes the total percentage of beam apertures for the various plans that could be delivered incorrectly without degrading plan quality below the set limit. These values ranged from 10–20% and were inversely proportional to the theoretical system response time.

4. Discussion

In this study, the treatment plan quality of 4D VMAT was investigated in comparison to gated VMAT and 3D VMAT for SBRT treatment of highly mobile lung tumours. When tumour
motion is involved in radiation therapy, there are three primary strategies available to reduce dose to healthy tissues. The first is to eliminate or minimize the motion encompassing margin used to ensure target coverage. The second is to temporally spread the instantaneous dose delivered to the tumour over its motion trajectory similar to how multiple beams are spatially used to prevent hot spots. The third is to optimize greater radiation dose delivery to respiratory phases that maximize the relative distance between the target and OARs. Table 7 provides a summary of the applicability of these three strategies to the treatment techniques of 3D VMAT, gated VMAT, and 4D VMAT. For a complete overview, characteristics of tracked VMAT were also included in table 7.

Gated VMAT can maximize the separation between target and OARs if the gating window occurs around max-inhale. However, for the majority of patients, this would lead to excessively extended treatment times. This study did not gate at max-inhale because it would have reduced the duty cycle from 40% to 20% for patient A, 60% to 10% for patient B and 50% to 10% for patient C. Despite planning near max-exhale, gated VMAT’s ability to spare the majority of the OARs was the greatest (section 3.1). 4D VMAT treated the tumour over its entire trajectory, but plan qualities were only slightly below those of gated VMAT because 4D VMAT was the only treatment technique that could exploit all three primary strategies (table 7). In fact, this study (section 3.1) and previous work by Chin and Otto (2011) showed that for certain anatomical deformations, 4D VMAT’s sparing of some OARs can be superior to other treatment deliveries such as gated VMAT.

For 3D VMAT, despite the care in maximizing the sparing of healthy tissues by avoiding the ITV margin concept, plan quality was the poorest for all three patients. Under the current SBRT protocol of 48 Gy in four fractions, all generated plans were clinically acceptable, including those by 3D VMAT. As a result from a practical perspective, 3D VMAT would be the treatment of choice because its delivery was the fastest and the simplest to execute. On the other hand, if OAR sparing was prioritized above all else or the clinician chose to escalate the dose, then the preferred treatment options would have been gated VMAT or 4D VMAT. Future improvements in the understanding of the radiobiological consequences (Li et al. 2012) may also alter the SBRT protocol to favour more complex treatments. This study was limited to three patients with large tumour motions (1.4–3.4 cm). The benefits of gated VMAT or 4D VMAT are less likely to be observed for tumour motions below 1 cm as expansion of treatment margins may only be in the range of a few millimetres (Guckenberger et al. 2009, 2011).

The main advantage of 4D VMAT was that while its plan quality was similar to gated VMAT, its treatment delivery time was less than a minute longer than 3D VMAT. There was some degradation in 4D VMAT plan quality when the MU$_{beam_{max}}$ constraint was enforced to ensure efficient delivery, but this problem can easily be solved with the higher dose rates of 1400–2400 MU min$^{-1}$ available in flattening filter free (FFF) beams (Ong et al. 2012).
Naturally with a higher dose rate, the relative difference in treatment times between 3D VMAT and 4D VMAT would disappear. Gated VMAT treatment times would also decrease but the frequent stops and starts of the gantry rotation would still be mechanically challenging for the linac.

Ideally, this study would have also included a comparison with tracked VMAT. Unfortunately, test simulations of a rigid DMLC tracked VMAT algorithm tended to lose target coverage because they did not account for the deformation of the GTV. This loss of target coverage in rigid tracking algorithms has also been found by others (Suh et al 2008b, 2009, Gui et al 2010). Tracked test simulations with marginally larger treatment margins obtained satisfactory GTV dose coverage, but OAR sparing was not competitive. A possible solution would be to create a deformable DMLC tracking algorithm (Papiez et al 2005, Gui et al 2010, Guo et al 2011), but that was beyond the scope of this work. Previous work (Chin and Otto 2011) did demonstrate that 4D VMAT was superior to tracked VMAT but was only verified in rigidly moving phantoms. Relative to comparisons with 3D VMAT and gated VMAT, comparing 4D VMAT to tracked VMAT was of lower importance because both are respiratory correlated techniques whose deliveries require a similar level of time, complexity and workload. 4D VMAT simply offers the possibility of better healthy tissue sparing by planning on 4D CT data instead of 3D CT data.

The strength and weakness of 4D VMAT treatment planning is the integration of a priori patient motion information into the plan optimization. The advantage is the higher quality treatment plans as all tissue motion is accounted for, but the disadvantage is the requirement that beam aperture delivery be synchronized to patient breathing and that the breathing pattern be reproducible. The robustness of 4D VMAT treatment plans to treatment desynchronization delivery errors was tested using an artificial setup. While it may not have mimicked the full range of breathing variability in real patients, a few important conclusions can still be made. First, 4D VMAT can be insensitive to some delivery errors. Of the total beam apertures, 10–20% could be delivered out of synchronization by a shift of two phases from their correlated phase without violating the threshold on plan quality. Second, the shorter the system latency in responding to treatment delivery errors, the more frequently the errors could occur. In table 6, the percentage of beams with delivery errors could be as much as 20% with a 1.2 s response time but only allowed 10% with a 2.4 s response time. This information may be useful for future designs of online image guidance systems.

The 4D VMAT plans were robust to some desynchronization delivery errors due to the limits placed on beam weight and MLC motion. The MUbeam_max constraint prevented major variation of MUs between beam apertures and was comparable to the robust technique of Nohadani et al (2010). The 4D VMAT algorithm also constrained the amount of allowed MLC leaf motion between beam apertures (Otto 2008) to avoid large changes in aperture shape and could be considered analogous to the robust strategy employed by Alasti et al (2006). Despite these constraints, the 4D VMAT plan qualities still compared well to the gated VMAT plans.

For future work, there are many possible avenues of investigation. With only 4D CT data, robustness testing of 4D VMAT plans was limited to desynchronization delivery errors in this study. Irregularities in tumour motion amplitude or shifts in tumour baseline position could not be investigated. Complete and realistic testing of the robustness of 4D VMAT treatment plans to all possible deviations requires the creation of a dynamic virtual patient model (Low et al 2005, Yang et al 2008, Eom et al 2010, McGurk et al 2010, Guo et al 2011). Not all deviations will have a meaningful effect on plan quality; therefore, action thresholds should also be established. The magnitude of these action thresholds will likely depend on the specific patient geometry and treatment plan (Zhang et al 2011b, 2012). Another consideration is that perfectly regular breathing motion may not actually be necessary for 4D VMAT delivery. The
current implementation of 4D VMAT did not allow for changing gantry speeds only because the dose rate of 600 MU min$^{-1}$ is too low to deliver the full MU of some beam apertures should the patient breathing accelerate. This is less likely to be a concern with the higher dose rates of FFF beams. The gantry rotation may then be allowed to change speeds to track patients with moderately irregular respiratory periods in a concept similar to MLC tracking for irregular breathing by Yi et al (2008). Lastly but most importantly, the 4D VMAT optimization must be updated with a faster and more accurate dose calculation algorithm. Promising options are GPU-based Monte Carlo or GPU-based finite-size pencil beams with 3D density corrections (Gu et al 2011, Jia et al 2011).

5. Conclusion

A breathing-synchronized 4D VMAT treatment technique incorporating patient motion information from 4D CT data directly into the optimization algorithm was used to generate SBRT treatment plans on three patients with NSCLC. Healthy tissue sparing of 4D VMAT plans were comparable to gated VMAT plans but with treatment delivery efficiencies closer to 3D VMAT. The current implementation of 4D VMAT requires treatment synchronization to reproducible patient motion but preliminary tests showed robustness to random and systematic desynchronized delivery errors. Future developments in respiratory tracking have the potential to adapt 4D VMAT to irregular patient breathing. 4DVMAT is a viable alternative to gated VMAT. It can allow for further dose escalation in SBRT lung treatments without the negative consequence of gated VMAT’s extended treatment time.

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