

Clinical use of Four-dimensional Computed Tomography Scans

a report by

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DOI: 10.17925/EOR.2005.0.0.1g

The Impact of Mobility on High-precision Radiotherapy

The goal of conformal radiation therapy is to precisely deliver high doses to the tumour while minimising doses to surrounding critical structures. Recent technical developments such as intensity-modulated radiotherapy (IMRT) have made it possible to deliver highly conformal radiation dose distributions to complex three-dimensional (3-D) target volumes. High-precision techniques, such as IMRT, stereotactic radiotherapy (SRT) and respiration-gated radiotherapy, are promising tools for dose escalation in the management of thoracic and abdominal lesions. One example is the local control rates in excess of 85% that were achieved for small peripheral lung tumours with SRT using biologically effective doses of 106 to 180Gy.^{1,2} However, tumours and organs in the thorax and upper abdomen can exhibit considerable mobility, leading to important errors between planned and delivered dose distributions. The inability to accurately characterise tumour and organ mobility for an individual patient remains a major impediment to the clinical application of high-precision radiotherapy.

Radiotherapy planning of tumours in the thorax and upper abdomen is commonly based on the use of a single computed tomography (CT) scan performed

during quiet respiration, in contrast to diagnostic CT scans, which are performed during breath-hold. The reason for performing CT scans during quiet respiration is to reproduce the situations during daily treatment that take place under similar conditions. However, this introduces artefacts that incorrectly characterise the geometric shape and extent of a structure.³ As has been demonstrated using phantom studies,⁴ the extent of artefacts depends on the interplay between CT slice acquisition and the asynchronous motion of different organs. This may result in tumours being imaged in two or more distinct parts, with the axial slices being shuffled out of order (see *Figure 1*). Furthermore, non-representative imaging using a conventional planning CT scan also leads to incorrect information on normal organ size and position, with inaccurate information on the actual dose-distribution in these structures. Respiration-induced organ motion greatly degrades the potential effectiveness of advanced treatment planning and delivery. Until recently, the problem of doses to mobile normal organs was largely ignored in routine practice, but standard 'safety' margins were added around tumours in order to ensure target coverage. Studies have shown that even these margins may be insufficient to account for extremes of mobility⁵⁻⁷ and may increase the risks of toxicity to surrounding organs, which in turn limits the total dose of radiotherapy.



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Individualised Approach to Tumour and Organ Mobility

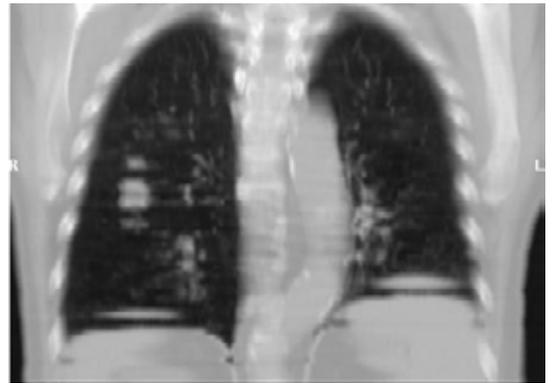
Individualised, i.e. patient-specific, margins are required to account for mobility as no clear correlation exists between mobility and anatomical location in the thorax.⁶⁻⁸ A major advance in this field is respiration-correlated (4-D) CT scanning in which spatial and temporal information on organ mobility are generated using cine scans, while the respiratory waveform is synchronously recorded during imaging. As multiple axial CT slices are acquired at each table position for at least the duration of one full respiratory cycle, this approach yields complete data on organ mobility in the prescribed trajectory. The clinical data described below was mainly generated on a 16-slice CT scanner during quiet uncoached respiration. During the scanning procedure, respiratory signals are recorded using Varian Real-Time Position Management (RPM) respiratory monitoring hardware. The RPM system uses infrared-reflecting markers mounted on a block that is placed on the upper abdomen. Advantage 4-D software was used to sort each CT image into one of 10 'bins' corresponding to the respiratory phase at which the image was captured. A 4-D CT scan is essentially a collection of 3-D CT volumes at all different respiratory phases in the patient, all of which is acquired in a single session. Such a full 4-D scan of the whole thorax is typically acquired within one to two minutes.

Other methods that have been described for acquiring co-registered respiratory signals include spirometry, nasal thermocouples and abdominal strain gauges. If 4-D information is to be used for gated treatment delivery, the method used to acquire respiratory information should also be present at the treatment unit.

Clinical Evaluation and Applications of 4-D CT

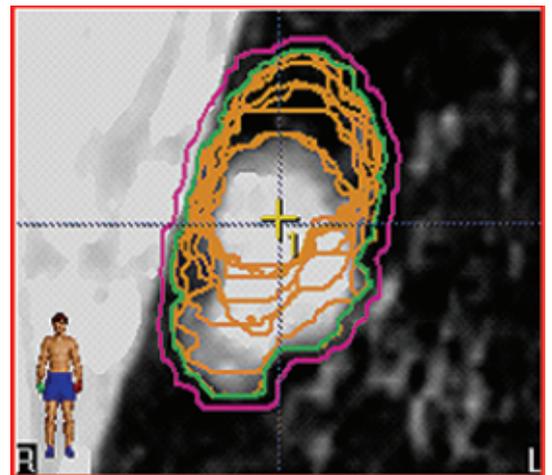
The problem of organ mobility is ideally approached using 4-D radiotherapy, which has been defined as the explicit inclusion of temporal changes in anatomy during imaging, planning and delivery of radiotherapy.⁹ However, 4-D planning software programmes are not yet commercially available, and techniques for on-board volumetric imaging at the treatment unit are only now entering clinical use. Nevertheless, the availability of 4-D CT information

Figure 1: Imaging Artefact of a Mobile Lung Tumour



The image of a single tumour in the right lung appears in four distinct parts in this spiral CT scan (one slice/second). The commonly observed distortion of the domes of the diaphragm are also evident.

Figure 2: A 4-D CT Plan Showing all Positions of a Peripheral Lung Tumour (yellow contours), with Only the Most Caudal Tumour Position Visible in this Image



A single conventional scan could have led to the use of inappropriate radiation fields. The internal target volume (green contour) encompasses all tumour positions, and the pink contour represents a planning target volume for stereotactic radiotherapy.

has been used to influence clinical treatment at a number of institutions in the following areas:

- identifying immobile tumours and reducing the mobility margins in such tumours;
- implementing 'conformal avoidance' of critical organs, such as the kidneys, by selecting treatment techniques that minimise such irradiation;
- determining the benefits of 'gated' radiotherapy for mobile tumours, and establishing individual

8. van Sömsen de Koste J R, Lagerwaard F J, Nijssen-Visser M R, et al., "Tumor location cannot predict the mobility of lung tumors: a 3D analysis of data generated from multiple CT scans", *Int. J. Radiat. Oncol. Biol. Phys.* (2003);56: pp. 348-354.

9. Keall P, "4-Dimensional computed tomography imaging and treatment planning", *Semin. Radiat. Oncol.* (2004);14: pp. 81-90.

margins for residual mobility within chosen respiratory ‘gates’; and

- determining reproducibility of tumour position after interventions that aim to reduce mobility, such as active-breathing control and deep-inspiration breath-holds, and checking its effectiveness.

Key aspects of the initial clinical experience with 4-D CT are briefly highlighted below.

Mobility Assessment Using 4-D CT Versus Multiple CT Scans

Because a single conventional CT scan may capture a random position of a mobile tumour, up to six such planning scans have been used for defining target volumes for peripheral lung tumours.^{10,11} However, the approach is lengthy, and all scans must be co-registered prior to the generation of target volumes. This cumbersome process contrasts with the use of a single 4-D CT scan to generate full spatial and temporal information on mobility in less than 1.5 minutes (on a 16-slice CT scanner). The internal tumour volumes, i.e. volumes that incorporate all tumour mobility, derived using a single 4-D CT scan (see *Figure 2*) were found to be similar to or (in 20% of cases) larger than those derived using six random uncoached CT scans.¹² However, since individual information on mobility patterns is available, margins to obtain the planning target volume can be reduced. In a series of 34 stage I lung cancer patients, the planning target volume was reduced, on average, by 48% compared with those obtained using standard techniques.⁷ These findings validated the assumptions underlying 4-D CT, and resulted in the technique being used as standard for thoracic and upper abdominal radiotherapy planning.

Mobility Assessment Using 4-D CT Versus Fluoroscopy

Fluoroscopy is widely used for evaluating tumour mobility in treatment planning for lung cancer. A recent study compared mobility measured from

contoured tumours in all phases of the 4-D CT scan with that scored using corresponding digitally-enhanced fluoroscopy by four clinicians.¹³ Clinicians systematically overestimated mobility using fluoroscopy. Moreover, it was found to be unsuitable for measuring mobility in at least one direction in 25% of the patients. These limitations, plus the fact that the mobility assessed by fluoroscopy cannot be linked to the geometry of a planning CT scan acquired without breathing registration, have led to the use of 4-D CT scanning being the standard approach for high precision stereotactic radiotherapy.

4-D Respiration-gated Radiotherapy

By irradiating mobile tumours during only a predetermined (and reproducible) phase of respiration, so-called ‘gated’ radiotherapy can ensure that the volume of irradiated normal tissues is minimised and accuracy of the dose-distribution is improved. The RPM system described above is an example of a technique originally developed for delivering gated radiotherapy. Reliable data on the correlation between 3-D tumour mobility and the respiratory cycle is essential. Many early reports on the technique exclusively used fluoroscopy for selecting appropriate phases for respiratory gating. The limitations of 2-D fluoroscopy are evident (see above), but 4-D CT datasets can allow for a full assessment of the benefits of gating. A planning study using 4-D CT data from 34 stage 1 non-small cell lung cancers (NSCLC) found that gating would have reduced planning target volumes (PTVs) by more than 50% in only 15% of tumours.⁷ The gains from gating were greatest in tumours showing mobility of 1cm or more, and such tumours comprised only a third of peripheral lung tumours. A similar study in patients with stage 3 NSCLC indicated that modest reductions in PTVs can be achieved using 4-D gating.¹⁴

Limiting the Workload Associated with 4-D CT Scanning

The time required for contouring tumours and/or normal organs in all 10 or more respiratory phases

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11. van Sornsens de Koste J R, Lagerwaard FJ, Schuchhard-Schipper R H, et al., “Dosimetric consequences of tumor mobility in radiotherapy of stage I non-small cell lung cancer- an analysis of data generated using ‘slow’ CT scans”, *Radioth. Oncol.* (2001);61: pp. 93–99.

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13. van der Geld Y, Senan S, van Sornsens de Koste J R, et al., “Determining lung tumor mobility for radiotherapy planning: A comparison of fluoroscopy and 4D CT data”, *Proceedings of the 11th World Conference on Lung Cancer, Barcelona, 3–6 July 2005.*

14. Underberg R W M, van Sornsens de Koste J R, Slotman B J, Senan S, “Respiration-gated radiotherapy in stage III NSCLC: an analysis of data generated using 4D CT scanning”, *Proceedings of the 11th World Conference on Lung Cancer, Barcelona, 3–6 July 2005.*

can be a major drawback to the routine clinical use of 4-D CT scans. Reliable auto-segmentation tools for contour generation are not yet available and remain the subject of active on-going research. To reduce the workload of contouring multiple target volumes in all phases of a 4-D CT, the post-processing tools of maximum intensity projections (MIP) and minimum intensity projections (MinIP) were evaluated.¹⁵ Briefly, an MIP is the maximum value of a pixel over all phases and indicates any location where the tumour is present over all phases. The MinIP is the minimum value of each pixel over all phases and indicates only those locations where tumour is constantly present over all phases. A target volume encompassing the separate targets in each phase of respiration in a 4-D CT scan, compared with that derived using a single MIP, showed similar results for patients with peripheral lung cancer. The generation and contouring of an MIP image requires less than 10 minutes per patient, and this technique can enable individualised internal target volumes to be derived from 4-D CT. Similarly, benefits of respiration-gated radiotherapy were also shown to correlate with the ratio of MIP to MinIP, which further reduces the time required to analyse 4-D CT scans.

On-going Research

Data acquired during a 4-D CT is very dependant on the respiratory pattern of patients. The authors' patients were scanned during uncoached, quiet respiration after a reproducible pattern of respiration was observed. Preliminary analysis of the movement

of abdominal organs suggests that mobility can vary according to the amplitude of the respiratory signal. It has been recommended that patients should undergo audio and/or visual coaching in order to ensure regular respiration during gated radiotherapy.¹⁶ Analysis of serial 4-D CT scans performed during treatment will establish the reproducibility of uncoached breathing patterns as well as their correlation with tumour position. However, a need to perform respiratory coaching for all patients prior to and during both 4-D CT acquisition and treatment delivery implies a greatly increased workload. Efforts to identify patients who will benefit from respiratory coaching and those in whom it can be omitted are now under way.

Another key area in the clinical development of 4D radiotherapy is the development of hardware and software protocols that will permit volumetric tracking of internal anatomy at the treatment unit. Ensuring that any drifts in the tumour position will be detected during treatment is essential for high precision radiotherapy of mobile tumours.

Conclusion

Four-dimensional or respiration-correlated CT scans represent a major advance in radiotherapy planning for tumours in the thorax and upper abdomen. Individualised target volumes can be generated for each patient with a potentially mobile tumour. Patients who may benefit from modified treatment delivery, such as respiratory gating, can be objectively identified. ■

15. Underberg R W M, Lagerwaard F J, Slotman B J, Cuijpers J P, Senan S, "Use of maximum intensity projections for target volume generation in 4DCT scans for lung cancer", *Int. J. Radiat. Oncol. Biol. Phys. In press.*

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