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Conventional 3D staging PET/CT in CT simulation for lung cancer: impact of rigid and deformable target volume alignments for radiotherapy treatment planning

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Objective: Positron emission tomography (PET)/CT scans can improve target definition in radiotherapy for non-small cell lung cancer (NSCLC). As staging PET/CT scans are increasingly available, we evaluated different methods for co-registration of staging PET/CT data to radiotherapy simulation (RTP) scans.
Methods: 10 patients underwent staging PET/CT followed by RTP PET/CT. On both scans, gross tumour volumes (GTVs) were delineated using CT (GTV_{CT}) and PET display settings. Four PET-based contours (manual delineation, two threshold methods and a source-to-background ratio method) were delineated. The CT component of the staging scan was co-registered using both rigid and deformable techniques to the CT component of RTP PET/CT. Subsequently rigid registration and deformation warps were used to transfer PET and CT contours from the staging scan to the RTP scan. Dice's similarity coefficient (DSC) was used to assess the registration accuracy of staging-based GTVs following both registration methods with the GTVs delineated on the RTP PET/CT scan.
Results: When the GTV_{CT} delineated on the staging scan after both rigid registration and deformation was compared with the GTV_{CT} on the RTP scan, a significant improvement in overlap (registration) using deformation was observed (mean DSC 0.66 for rigid registration and 0.82 for deformable registration, $p=0.008$). A similar comparison for PET contours revealed no significant improvement in overlap with the use of deformable registration.
Conclusions: No consistent improvements in similarity measures were observed when deformable registration was used for transferring PET-based contours from a staging PET/CT. This suggests that currently the use of rigid registration remains the most appropriate method for RTP in NSCLC.

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18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/CT scanning is now a standard procedure for staging patients with non-small cell lung cancer (NSCLC) [1]. PET/CT imaging is also beneficial in radiotherapy treatment planning (RTP), for example by identifying metastases to mediastinal lymph nodes. PET/CT for RTP simulation has also been shown to reduce interobserver variation in gross tumour volume (GTV) delineation [2, 3].

Metabolic information can be incorporated into the RTP process by performing a dedicated RTP PET/CT simulation with the patient positioned in the treatment position and on a flat couch top [4, 5]. This approach is superior to using CT alone for simulation, followed by visual correlation with PET [3]. However, acquiring a second PET/CT scan involves extra costs as well as increasing the radiation dose to the patient and the staff involved in the scanning procedure owing to the administration of a second dose of radiopharmaceutical [6]. As staging PET/CT scans are increasingly available in patients who are referred for radiotherapy, other investigators have described methods of co-registering staging PET/CT and RTP CT simulation scans [7]. However, diagnostic scanning protocols are usually acquired on a curved couch top, and differences in anatomical positioning may hinder accurate co-registration. Positioning a patient in the radiotherapy treatment position during the staging PET scan acquisition, by use of a flat table insert, improves the accuracy of rigid registration of staging and RTP CT scan [8].

Deformable registration seeks to reduce potential differences between imaging data sets, such as differences in anatomical positioning, by estimating the spatial relationship between volume elements of the scan sets, while maintaining the modality-specific information [9]. The correct estimation of these differences may permit the accurate transfer of radiotherapy target volume structures between image data sets. The use of deformable

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registration has been shown to allow for more accurate registration of a staging PET/CT scan to a RTP CT scan in patients with head and neck tumours [10, 11]. However, caution has been advised as the benefits of using deformable registration for this purpose for thoracic tumours is unproven [12]. In the present study, we assess the accuracy of both rigid and deformable registration for transferring target volumes delineated on a staging PET/CT scan to a RTP scan in NSCLC.

Methods

Patient selection

Between November 2004 and June 2007, a study, approved by the ethics committee, at the Northern Ireland Cancer Centre, Belfast, enrolled patients with pathologically proven, inoperable NSCLC, Stages I–IIIB (American Joint Committee on Cancer Staging) [13]. Eligible patients had a prior staging 18F-FDG PET/CT scan [3]. Included in this investigation were patients treated with radiation alone and having a maximum time of 9 weeks between staging and RTP PET/CT scans.

Staging PET/CT scan acquisition

Both staging and RTP PET/CT scans were acquired using the same General Electric Discovery Lightspeed Combined PET/CT scanner (GE Medical System, Milwaukee, WI). For the staging scans, patients were positioned on the standard diagnostic curved couch top, with arms raised above the patient's head. An intravenous injection of 18F-FDG (375 MBq) was followed by a minimum 45 min uptake period. Transmission CT scanning followed by emission PET scanning was undertaken from above the vertex of the skull to the mid-thigh level. A standard diagnostic imaging protocol was used and no special breathing instructions were given during the CT acquisition. In keeping with the institutional protocol, no intravenous contrast was used during CT acquisition.

RTP PET/CT scan acquisition

The RTP PET/CT scan was performed with the patients immobilised using a locally modified Med-TEC thorax immobilisation board (Med-TEC, Orange City, IA) and a knee rest [14]. The immobilisation board was positioned on a flat-top couch insert. After an intravenous injection of 18F-FDG (375 MBq), followed by a 45 min uptake period, patients were scanned in the treatment position with both arms raised above their head. A standard diagnostic imaging protocol identical to that used in the staging scan acquisition was used and no special breathing instructions were given during the CT acquisition. No intravenous contrast was used during CT acquisition and image acquisition was confined to the thorax. To confirm that there was no significant misregistration or patient movement between the CT and PET components of the scan, visual inspection of the image data set after scanning was performed by the technologists acquiring the images.

Target volume delineation

On both the staging and RTP PET/CT scans, target volumes were delineated using Velocity AI (Velocity Medical Solutions, Version 2.1.1, Atlanta, GA). Delineation was undertaken by a single radiation oncologist with a special interest in lung cancer. Using the CT images alone the GTV of the primary tumour alone (GTV_{CT}) was delineated using standardised lung (Width (W) = 100, Centre (C) = −700) and mediastinal window (W = 350, C = 40) settings. Given that no single optimal method of PET-based target volume delineation in lung cancer exists, four different methods of PET-based target volume PET delineation were used [15]. The four PET-based contour delineation methods included:

- A manual PET contour (GTV_{PETMAN}) was generated following delineation using a standardised window setting, with the window width equal to the maximum of the pixel intensity within the target image and the window level equal to half this maximum [3].
- Two absolute threshold PET contours were delineated using an absolute standardised uptake value (SUV) threshold of 2.5 ($GTV_{SUV2.5}$) and a threshold of 35% ($GTV_{35\%SUVMAX}$) of the maximal SUV within the target image (SUV_{MAX}) [16, 17].
- A fourth PET contour (GTV_{PETSBR}) used a modification of the source-to-background algorithm as described by Boellaard et al [18]. In the first instance, a region of interest (ROI) around the tumour volume was defined and the SUV_{MAX} within this ROI was measured. Then the mean SUV of the background activity in tissue surrounding the tumour was measured. Finally, the threshold defining the GTV_{PETSBR} is given by the following equation:

$$\text{Threshold} = (0.42 \times (\text{SUV}_{\text{MAX}} + \text{mean SUV in background})) \quad (1)$$

Rigid and deformable registration of staging PET/CT scan to RTP PET/CT scan

As both scans were obtained using an inline PET/CT scanner, the PET and CT scan components automatically share Digital Imaging and Communications in Medicine (DICOM) coordinates. Thus, additional co-registration is not needed as patients are not repositioned during these scan acquisitions and no major misalignment was detected. Given the low resolution of the PET images and the lack of clear discernable normal landmarks, all registration was undertaken using the CT components of the staging and planning PET/CT scans. Registration of the PET scans was therefore performed using the same registration parameters of the CT to CT-based registration. For CT–CT registration, initially, a rigid registration focusing on the dorsal spine was undertaken using the Velocity AI application.

Following rigid registration, image deformation, using Velocity AI, was then performed. In this process the CT components of the PET/CT scans were deformed to the CT of the planning scan using a modified basis spline (B-spline) registration algorithm combined with the Mattes

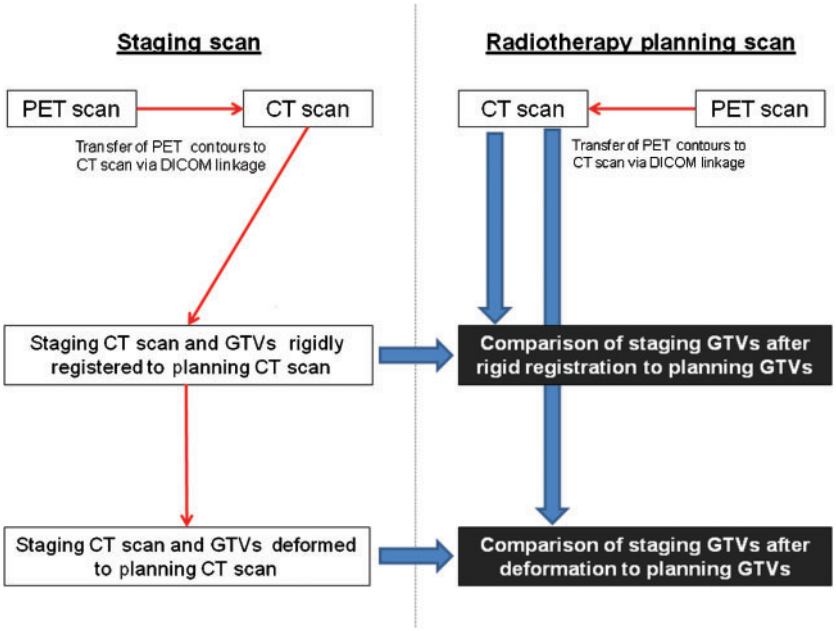

Figure 1. Schema of registration of the CT component of the staging positron emission tomography (PET)/CT scan to radiotherapy planning PET/CT scan, transfer of gross tumour volume (GTV) contours and comparison of delineated volumes.

[19] formulation of the mutual information metric. Deformable registration is an optimisation process that aims to recover the unknown parameters of any transformation that is required to correlate matching anatomic features observed in two different scan images of the same patient. An interactive iterative process is used to modify the transformation parameters until an optimal match is found between the scan images. In the current study deformable registration was performed using default software settings using a coarse grid with a maximum deformation distance of 50 mm. A three-step deformation was employed with the initial deformable registration that involved the entire lung volume, followed by two additional deformable registrations restricted to the tumour-bearing region, including a sufficient amount of surrounding lung tissue and sometimes including adjacent chest wall or vertebra, depending on the location of the tumour. In a recent comparison of deformation

Table 1. Gross tumour volume (GTV) contour nomenclature at each step of registration

Staging PET/CT scan outlines	Staging PET/CT scan outlines after rigid registration to RTP PET/CT scan	Staging PET/CT scan outlines after deformable registration to RTP PET/CT scan	RTP PET/CT scan outlines
$GTV_{CT}^{STAGING}$	GTV_{CT}^{RIGID}	GTV_{CT}^{DEFORM}	GTV_{CT}^{RTP}
$GTV_{PETMAN}^{STAGING}$	GTV_{PETMAN}^{RIGID}	GTV_{PETMAN}^{DEFORM}	GTV_{PETMAN}^{RTP}
$GTV_{SUV2.5}^{STAGING}$	$GTV_{SUV2.5}^{RIGID}$	$GTV_{SUV2.5}^{DEFORM}$	$GTV_{SUV2.5}^{RTP}$
$GTV_{35\%SUVMAX}^{STAGING}$	$GTV_{35\%SUVMAX}^{RIGID}$	$GTV_{35\%SUVMAX}^{DEFORM}$	$GTV_{35\%SUVMAX}^{RTP}$
$GTV_{PETSBR}^{STAGING}$	GTV_{PETSBR}^{RIGID}	GTV_{PETSBR}^{DEFORM}	GTV_{PETSBR}^{RTP}

GTV, gross tumour volume; PET, positron emission tomography; RTP, radiotherapy treatment planning; SUV, standardised update value.

Table 2. Baseline tumour characteristics

Patient no.	Stage	Side	Lobe	Position	Pathology	Staging PET/CT SUV_{MAX}	RTP PET/CT SUV_{MAX}
1	IB	Right	Middle	Peripheral	NSCLC	11.4	11.6
2	IB	Left	Lower	Central	Squamous	12.9	10.3
3	IIIB	Right	Upper	Central	Squamous	11.6	11.8
4	IIIA	Right	Lower	Peripheral	Squamous	15.6	15.1
5	IA	Left	Upper	Peripheral	Squamous	10.8	10.3
6	IIIB	Right	Upper	Central	Squamous	11.1	10.0
7	IA	Left	Lower	Peripheral	NSCLC	6.7	8.1
8	IIIB	Right	Upper	Peripheral	Squamous	16.6	15.6
9	IIB	Right	Upper	Peripheral	NSCLC	12.2	12.2
10	IB	Right	Upper	Peripheral	NSCLC	6.4	7.2

NSCLC, non-small cell lung cancer; PET, positron emission tomography; RTP, radiotherapy treatment planning; SUV, standardised uptake value.

techniques, the B-spline local deformation technique used in this investigation had the smallest error of the various deformation methods investigated [20].

Transfer of target volumes using rigid and deformable registration

The GTV_{CT}, $GTV_{PETMAN,}$ $GTV_{SUV2.5}$, $GTV_{35\%SUVMAX}$ and the GTV_{PETSBR} contours delineated on the staging PET/CT scan set were transferred to the RTP PET/CT scan set using:

(a) a linear transformation with the same displacements and rotations used in the rigid registration process between the CT data sets;
(b) the ''warp'' arrived at in the deformation process and using the same three-dimensional (3D) displacement vectors between the CT data sets.

A schema of the registration steps and transfer of contours is illustrated in Figure 1 and the nomenclature of the GTV_{CT} and the four PET-based GTV contours is detailed in Table 1.

Table 3. Measurements (ml) of the gross tumour volume (GTV) on the staging positron emission tomography (PET)/CT scan, after rigid registration, after deformable registration and the GTV as delineated on the radiotherapy treatment planning (RTP) PET/CT scan

Patient	Delineation method	GTV on staging scan (ml)	GTV from staging scan after rigid registration (ml)	GTV from staging scan after deformable registration (ml)	GTV on RTP scan (ml)
1	$GTV_{35\%SUVMAX}$	16.0	16.0	20.2	21.2
	GTV_{PETSBR}	12.4	12.4	15.7	16.3
	GTV_{PETMAN}	22.0	22.0	28.8	31.5
	$GTV_{SUV2.5}$	23.3	23.3	30.5	31.1
	GTV_{CT}	20.8	20.8	26.0	25.0
2	$GTV_{35\%SUVMAX}$	16.1	16.2	12.7	19.4
	GTV_{PETSBR}	8.8	8.8	6.8	11.8
	GTV_{PETMAN}	30.0	30.0	24.1	22.7
	$GTV_{SUV2.5}$	36.7	36.7	29.6	32.2
	GTV_{CT}	46.4	46.4	36.0	20.8
3	$GTV_{35\%SUVMAX}$	35.8	35.8	34.5	57.8
	GTV_{PETSBR}	26.3	26.3	25.9	37.9
	GTV_{PETMAN}	48.8	48.8	50.4	59.9
	$GTV_{SUV2.5}$	53.6	53.6	54.4	103.8
	GTV_{CT}	39.3	39.3	40.7	50.9
4	$GTV_{35\%SUVMAX}$	107.1	107.1	101.3	106.5
	GTV_{PETSBR}	80.2	80.2	75.6	71.6
	GTV_{PETMAN}	146.9	146.9	139.3	141.8
	$GTV_{SUV2.5}$	181.1	181.1	173.6	163.3
	GTV_{CT}	101.3	101.3	95.0	98.9
5	$GTV_{35\%SUVMAX}$	8.4	8.4	8.4	7.7
	GTV_{PETSBR}	5.8	5.8	5.9	5.3
	GTV_{PETMAN}	13.2	13.2	12.9	10.4
	$GTV_{SUV2.5}$	12.7	12.7	12.5	11.2
	GTV_{CT}	7.2	7.2	7.5	5.6
6	$GTV_{35\%SUVMAX}$	10.9	10.9	9.2	11.9
	GTV_{PETSBR}	6.3	6.3	5.3	6.7
	GTV_{PETMAN}	13.2	13.2	11.1	9.2
	$GTV_{SUV2.5}$	22.1	22.1	19.9	21.8
	GTV_{CT}	20.4	20.4	18.5	17.8
7	$GTV_{35\%SUVMAX}$	14.0	14.0	12.7	10.0
	GTV_{PETSBR}	8.0	8.0	7.7	5.8
	GTV_{PETMAN}	11.6	11.6	10.5	11.2
	$GTV_{SUV2.5}$	12.4	12.4	11.2	12.0
	GTV_{CT}	3.7	3.7	3.6	4.5
8	$GTV_{35\%SUVMAX}$	57.8	57.8	86.9	130
	GTV_{PETSBR}	46.2	46.2	66.0	46.1
	GTV_{PETMAN}	73.9	73.9	107.9	64.3
	$GTV_{SUV2.5}$	99.1	99.1	138.4	120.4
	GTV_{CT}	81.7	81.7	128.8	134.8
9	$GTV_{35\%SUVMAX}$	22.9	22.9	24.0	27.0
	GTV_{PETSBR}	17.0	17.0	17.6	14.9
	GTV_{PETMAN}	33.2	33.2	34.9	37.3
	$GTV_{SUV2.5}$	38.1	38.1	40.4	45.4
	GTV_{CT}	33.4	33.4	35.7	37.2
10	$GTV_{35\%SUVMAX}$	8.3	8.3	16.0	18.8
	GTV_{PETSBR}	5.3	5.3	11.7	13.5
	GTV_{PETMAN}	7.9	7.9	15.6	18.8
	$GTV_{SUV2.5}$	7.0	7.0	14.3	18.1
	GTV_{CT}	6.3	6.3	13.2	15.4

Table 4. Displacement of centre of mass (mm) between the gross tumour volume (GTV) contours on the staging positron emission tomography (PET)/CT scan when registered using both rigid and deformable approaches with the CT component of the simulation PET/CT scan when compared with contours obtained using the simulation PET/CT scan alone

Patient	Comparison	Vector size (mm) between centre of mass of GTV from staging scan after rigid registration or deformation to RTP scan and the centre of mass on the RTP scan				
		$GTV_{35\%SUVMAX}$	GTV_{PETSBR}	GTV_{PETMAN}	$GTV_{SUV2.5}$	GTV_{CT}
1	Staging GTV after RIGID registration with RTP GTV	9.3	13.7	8.6	8.5	3.6
	Staging GTV after DEFORMATION with RTP GTV	10.0	8.4	11.0	8.4	2.2
2	Staging GTV after RIGID registration with RTP GTV	2.4	3.7	1.4	2.0	13.2
	Staging GTV after DEFORMATION with RTP GTV	17.7	17.7	13.2	13.3	3.7
3	Staging GTV after RIGID registration with RTP GTV	13.8	13.0	13.8	15.2	4.6
	Staging GTV after DEFORMATION with RTP GTV	12.1	10.0	10.0	13.0	3.6
4	Staging GTV after RIGID registration with RTP GTV	4.3	4.3	9.1	7.1	2.2
	Staging GTV after DEFORMATION with RTP GTV	5.2	4.8	7.6	9.7	4.8
5	Staging GTV after RIGID registration with RTP GTV	1.5	2.4	2.5	2.4	1.4
	Staging GTV after DEFORMATION with RTP GTV	2.3	4.4	4.3	4.3	2.5
6	Staging GTV after RIGID registration with RTP GTV	5.0	3.2	3.1	7.7	15.4
	Staging GTV after DEFORMATION with RTP GTV	3.7	4.3	2.5	6.3	9.9
7	Staging GTV after RIGID registration with RTP GTV	6.1	7.1	5.7	4.9	4.4
	Staging GTV after DEFORMATION with RTP GTV	3.9	7.7	6.3	5.7	1.5
8	Staging GTV after RIGID registration with RTP GTV	15.7	20.8	18.8	16.1	17.1
	Staging GTV after DEFORMATION with RTP GTV	11.7	11.0	9.7	8.5	4.1
9	Staging GTV after RIGID registration with RTP GTV	4.9	3.2	3.6	3.6	4.7
	Staging GTV after DEFORMATION with RTP GTV	5.2	4.9	2.9	3.6	2.2
10	Staging GTV after RIGID registration with RTP GTV	10.0	3.2	4.7	4.9	2.2
	Staging GTV after DEFORMATION with RTP GTV	5.2	4.9	5.2	5.8	1.1

Table 5. Dice's similarity coefficient measurements between contours on the staging positron emission tomography (PET)/CT scan using both rigid and deformable co-registration to the CT component of the simulation PET/CT scan when compared with contours derived using only the simulation PET/CT scan alone

Patient	Comparison	Dice's similarity coefficient measurements between GTV from staging scan after rigid registration or deformation to the RTP scan and the GTV on the RTP scan				
		$GTV_{35\%SUVMAX}$	GTV_{PETSBR}	GTV_{PETMAN}	$GTV_{SUV2.5}$	GTV_{CT}
1	Staging GTV after RIGID registration with RTP GTV	0.59	0.57	0.64	0.64	0.78
	Staging GTV after DEFORMATION with RTP GTV	0.65	0.68	0.69	0.67	0.86
2	Staging GTV after RIGID registration with RTP GTV	0.81	0.74	0.80	0.83	0.50
	Staging GTV after DEFORMATION with RTP GTV	0.40	0.32	0.52	0.56	0.72
3	Staging GTV after RIGID registration with RTP GTV	0.75	0.77	0.80	0.67	0.83
	Staging GTV after DEFORMATION with RTP GTV	0.72	0.76	0.78	0.67	0.82
4	Staging GTV after RIGID registration with RTP GTV	0.81	0.69	0.83	0.83	0.88
	Staging GTV after DEFORMATION with RTP GTV	0.81	0.72	0.82	0.83	0.91
5	Staging GTV after RIGID registration with RTP GTV	0.86	0.83	0.83	0.86	0.76
	Staging GTV after DEFORMATION with RTP GTV	0.71	0.65	0.77	0.77	0.82
6	Staging GTV after RIGID registration with RTP GTV	0.75	0.72	0.75	0.63	0.45
	Staging GTV after DEFORMATION with RTP GTV	0.73	0.74	0.74	0.74	0.63
7	Staging GTV after RIGID registration with RTP GTV	0.56	0.58	0.68	0.59	0.55
	Staging GTV after DEFORMATION with RTP GTV	0.77	0.52	0.63	0.79	0.79
8	Staging GTV after RIGID registration with RTP GTV	0.34	0.10	0.20	0.42	0.39
	Staging GTV after DEFORMATION with RTP GTV	0.53	0.49	0.55	0.67	0.80
9	Staging GTV after RIGID registration with RTP GTV	0.80	0.41	0.83	0.82	0.87
	Staging GTV after DEFORMATION with RTP GTV	0.79	0.41	0.83	0.83	0.90
10	Staging GTV after RIGID registration with RTP GTV	0.62	0.56	0.59	0.56	0.58
	Staging GTV after DEFORMATION with RTP GTV	0.72	0.72	0.72	0.70	0.86

Comparison of volumes and statistical analysis

The target volumes from the staging PET/CT scan transferred using rigid registration and using deformable registration were compared with the same contours on the RTP PET/CT scan. The percentage volume change (PVC) in the GTV from the staging scan at the different steps of registration with the same GTV type on the RTP scan was calculated. To assess positional change the 3D vector distance between the centre of mass (COM) of the GTV before and after each registration step and the GTV on the RTP scan was derived. Dice's similarity coefficient (DSC), assessing volumetric shape and positional change in a single measure, was calculated between the staging GTVs during and after the registration steps and the same GTV on the RTP scan. DSC, for the ratio of overlap between volumes A and B, is given by [21, 22]:

$$Dice's \quad similarity \quad coefficient = \frac{2(A \cap B)}{A + B} \qquad (2)$$

Descriptive statistics and paired *t*-tests (two-tailed) were used to examine any differences between data pairs and significance was reached for *p*-values being <0.05.

Results

Characteristics of the 10 patients included in this analysis are listed in Table 2. In all PET/CT scans reviewed, visual inspection revealed no major misalignment between the CT and PET components. The GTVs on staging and RTP PET/CT scans and at both steps of image registration are listed in Table 3. Patients 3, 8 and 10 had an increase of 25% or more in the GTV_{CT} between staging and RTP scans. Of note, Patients 3 and 8 had distal atelectasis. Results obtained for the COM and DSC analysis for all patients are listed in Tables 4 and 5.

Comparing the differences between the staging GTV_{CT} following rigid registration and deformable registration and the GTV_{CT} on the RTP scan (GTV_{CT}^{RIGID} with the GTV_{CT}^{RTP} and the GTV_{CT}^{DEFORM} with the GTV_{CT}^{RTP}) the GTV_{CT}^{DEFORM} had greater overall positional and volumetric similarity with the GTV_{CT}^{RTP}. In the comparison of GTV_{CT} contours the use of deformable registration resulted in a greater reduction in the COM displacement in 8 of the 10 patients, and an improvement in DSC for 9 of the 10 patients compared with rigid registration alone. For all patients the mean DSC assessing GTV_{CT} improved from 0.66 (GTV_{CT}^{RIGID} with the GTV_{CT}^{RTP}) to 0.82 (GTV_{CT}^{DEFORM} with the GTV_{CT}^{RTP}) ($p=0.008$). However the reduction observed in the mean COM displacement, from 6.9 mm (GTV_{CT}^{RIGID} with the GTV_{CT}^{RTP}) to 3.6 mm (GTV_{CT}^{DEFORM} with the GTV_{CT}^{RTP}) failed to reach significance ($p=0.056$). The mean percentage volume change between the GTV_{CT}^{RIGID} and the GTV_{CT}^{RTP} was 33.5% and this was reduced to a percentage volume change of 18.2% between the GTV_{CT}^{DEFORM} and the GTV_{CT}^{RTP} following deformation ($p=0.042$), again showing an improved approximation to the planning CT scan using deformation over rigid registration for CT-based contours. In marked contrast, all four PET-based target volumes revealed no similar improvements in registration with deformation over rigid registration. The mean DSC and COM displacements did not demonstrate any significant improvement, with the mean values listed in Figures 2 and 3.

Visual assessments of registration steps for the GTV contours revealed that, for those patients in whom there was a clear improvement in volume correlation for GTV_{CT} but a reduction in DSC for the PET-based contours (GTV_{PETSBR}, $GTV_{SUV2.5}$, $SUV_{35\%SUVMAX}$, GTV_{PETMAN}), the caudiocranial position of the GTV_{CT} in relation to the PET-based contours was in a different position on the staging scan from that on the RTP scan. An example from Patient 2 is illustrated in Figure 4.

To exclude the possibility that data from 3 patients with sizeable changes in tumour volume between staging and RTP scans (Patients 3, 8 and 10) resulted in poor results for the use of deformable registration, repeat DSC analysis

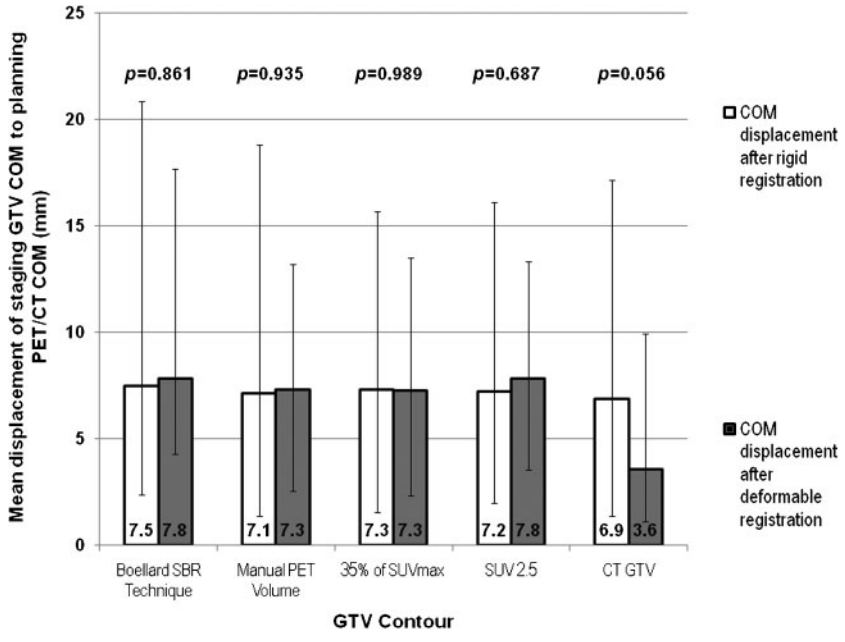

Figure 2. Mean centre of mass (COM) displacements from the staging gross tumour volumes (GTVs) after rigid and deformable registration to the planning positron emission tomography (PET)/CT scan GTVs. The range is denoted by the error bars, the mean values are shown and the two-tailed significance is listed above each comparison. The mean COM displacement is either increased or not improved after rigid registration for the four PET-based GTVs, suggesting a worsening or no improvement of registration with deformation. However, a reduction in COM for the GTV_{CT} suggests an improvement of registration for this target volume. SUV, standardized uptake value; SBR, source-to-background ratio.

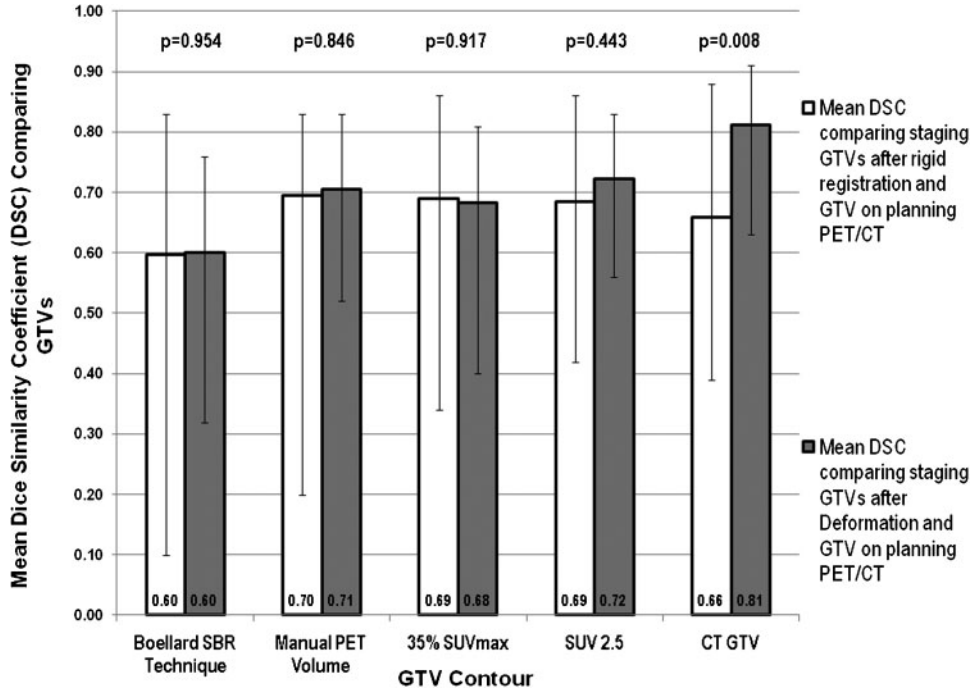

Figure 3. Mean Dice's similarity coefficients (DSCs) comparing the various gross tumour volumes (GTVs) after rigid and deformable registration with the same GTVs obtained on the planning positron emission tomography (PET)/CT scan. The range is denoted by the error bars, the mean values are shown and the two-tailed significance is listed above each comparison. There was no significant improvement in DSC with deformation over rigid registration for the four PET-based contours, suggesting no sizeable improvement in position or volume approximation with deformation. There is a significant increase in the mean DSC for the CT-based contour (GTV_{CT}), indicating a mean improvement in alignment and volume with deformation. SUV, standardised uptake value; SBR, source-to-background ratio.

using data from only the remaining 7 patients was performed, and it revealed no differences. For the seven patients without sizeable volume changes, the mean DSC assessing GTV_{CT} improved significantly from 0.69 (GTV_{CT}^{RIGID} with the GTV_{CT}^{RTP}) to 0.80 (GTV_{CT}^{DEFORM} with the GTV_{CT}^{RTP}) (p=0.001). However, DSC measurements comparing the PET-based contours for these patients did not improve (GTV_{PETSBR} p=0.491, $GTV_{SUV2.5}$ p=0.946, $SUV_{35\%SUVMAX}$ p=0.804, GTV_{PETMAN} p=0.370).

Discussion

In this investigation, we have demonstrated that deformable registration improves the overlap of GTV contours transferred from a staging to a planning CT scan. A significant improvement was seen in DSC (p=0.008) between the comparison of GTV_{CT}^{RIGID} with GTV_{CT}^{RTP} and the comparison of GTV_{CT}^{DEFORM} with GTV_{CT}^{RTP}. The observed improvement (*i.e.* reduction) in COM displacements following deformation also suggests that the deformation algorithm used has a benefit over rigid registration alone for CT-based registration. In contrast, similar improvements were not observed using deformable registration for transferring PET-based contours from the staging PET/CT scan, using the CT-based registration to the RTP PET/CT scan as an intermediate step. In a number of patients, the use of deformation led to an increase in COM displacement and a reduction in DSC (Tables 4 and 5).

Limited patient numbers

This study has a number of limitations which must be acknowledged. As our analysis was limited to only 10 patients, we may have missed a significant beneficial effect of deformable registration for the PET-based contours. Nevertheless, it was possible to demonstrate a significant improvement in DSC and volumetric approximation in this patient cohort for the CT-based contours and this has been demonstrated in other investigations [20].

Time delay between staging and planning scan acquisitions

A second notable limitation is the variable time scan between the staging and RTP PET/CT scan acquisitions for the patients studied. This variable time frame was often due to a complex referral and assessment pathway. Many of the patients included were initially considered for surgical resection, but were deemed not suitable or fit enough for surgical resection and the assessment for operability introduced delay between staging and RTP scan acquisitions. This variable time frame may permit sizeable tumour growth and hence apparent misregistration, given that this investigation only compared the primary target volume. Ideally, to exclude this source of error, comparison of two PET/CT scans no more than a day apart would be desirable. However, despite sizable GTV changes between the staging and RTP PET/CT

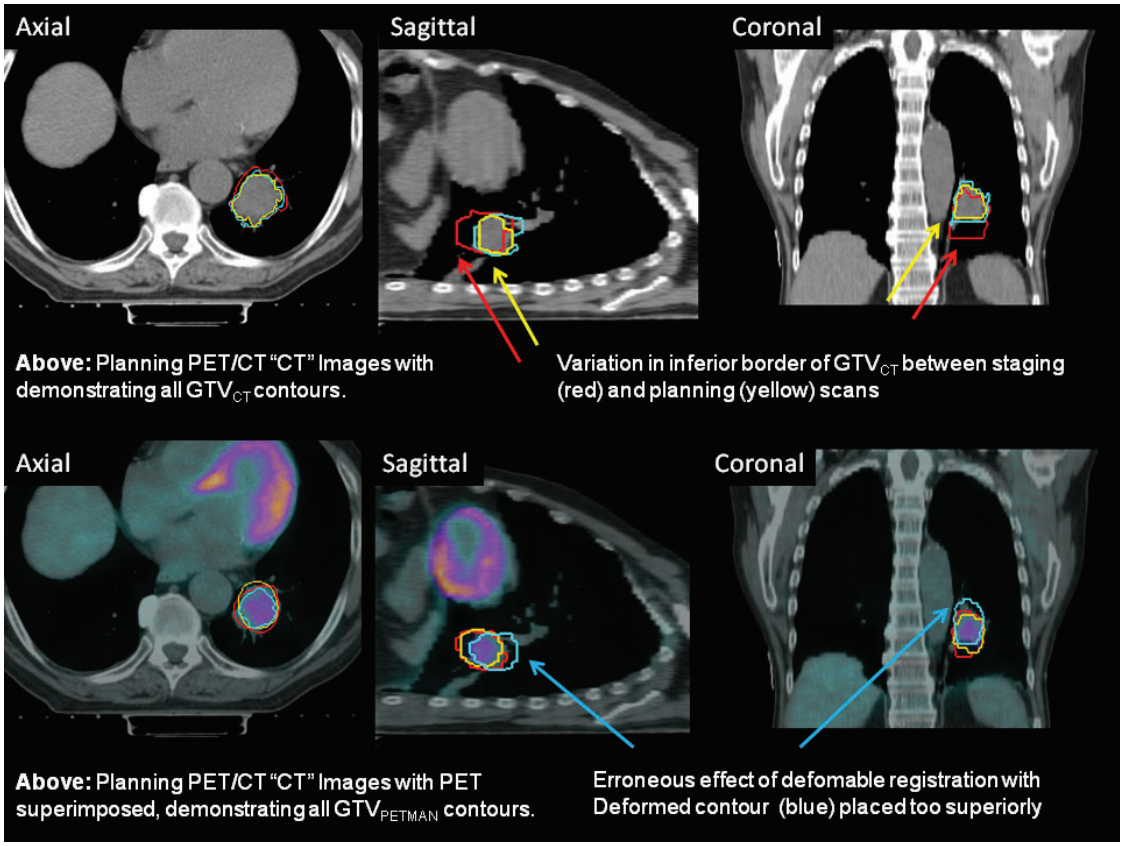

Figure 4. Axial, sagittal and coronal images from the planning positron emission tomography (PET)/CT scan acquired for Patient 2. The upper three images show the CT images alone with the three CT-based (GTV_{CT}) contours. The GTV_{CT}^{RTP} is yellow, the GTV_{CT}^{RIGID} is red and the GTV_{CT}^{DEFORM} is blue. Note the contrasting positions and inferior borders of the GTV_{CT}^{RTP} and the GTV_{CT}^{RIGID}. This may be due to the scan acquisitions being in different phases of the respiratory cycle. CT-based deformation correctly adjusts for that, aligning the GTV_{CT}^{DEFORM} in close approximation to the GTV_{CT}^{RTP}. However, if the scans were acquired in different respiratory phases, then the GTV_{CT} positions relative to PET contours will be different. In the lower three images the GTV_{PETMAN}^{RTP} is yellow, the GTV_{PETMAN}^{RIGID} is red and the GTV_{PETMAN}^{DEFORM} is blue. The rigid registration gives reasonable visual correlation with the GTV_{PETMAN}^{RTP}, although there is poor correlation between the GTV_{PETMAN}^{DEFORM} and the GTV_{PETMAN}^{RTP} contours.

scans for three patients, for the other seven patients the GTV size on both scans was similar, suggesting that no sizeable tumour progression (as assessed on CT) occurred. Although changes in tumour size may have an impact on simple volume comparisons, any such impact on COM and DSC comparisons should be minimal as was demonstrated by the similar DSC results when the three patients with sizeable volume differences (Patients 3, 8 and 10) were excluded.

Target volume delineation

The use of target volumes as the comparator to assess the accuracy of the registration technique has two potential limitations. Given that some target volumes were manually delineated (GTV_{CT} and GTV_{PETMAN}), possible intraclinician contouring variation between the scan sets may have led to variable comparisons between the CT and PET components. In this investigation it was hoped that the use of a single clinician for target volume delineation and the use of standardised windowing displays would minimise the potential variability that manual contouring may incur. In addition, the two PET threshold delineation methods ($GTV_{SUV2.5}$ and $GTV_{35\%SUVMAX}$) and the automated source-to-background ratio (SBR) delineation technique (GTV_{SBR}) used in our study showed very similar results to the GTV_{PETMAN} following rigid and deformable registration. Another limitation of using target volumes as the comparator of the registration similarity is that the results may have been influenced more by changes in the target volume alone, rather than the effect of the registration technique. However, compared with CT-based registration comparisons, thoracic PET scans have a paucity of clearly defined discrete anatomical landmarks on which to assess the accuracy of the registration technique. Hence, in this investigation, we chose to use the most clearly defined thoracic PET structure of relevance, namely the GTV as defined by four different PET-based delineation techniques.

Some possible reasons for a lack of benefit of deformable registration for PET contours can be considered. This may have been due to initial misalignment between the PET and CT components of each PET/CT scan, owing to patient movement between the CT and PET scan acquisitions. However, visual assessment did not reveal the former in this data set. In the studies investigating the use of deformable registration in head and neck cancer, the images obtained were of a static region of the body and for the planning CT scans the patient was immobilised in a custom-made shell [10, 11]. Owing to the effects of cardiac and respiratory

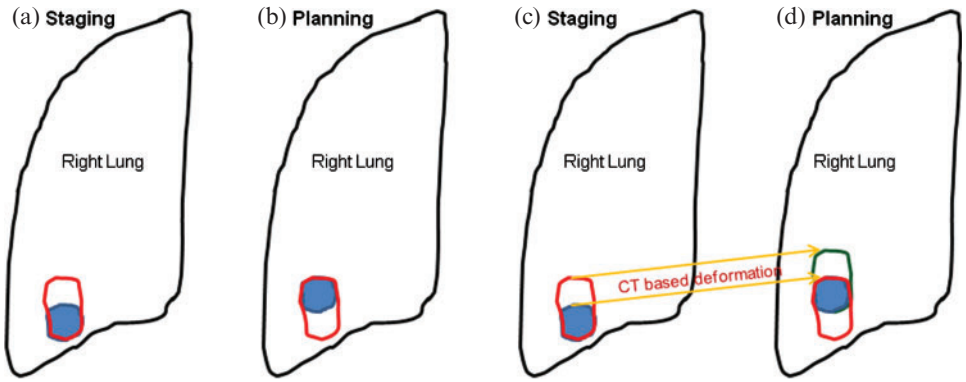

Figure 5. Visual explanation for poor performance of deformation of positron emission tomography (PET)-based contours due to differences in respiratory motion between the scans. The relationship between (a) and (b) is analogous to rigid registration and the relationship between (c) and (d) is analogous to deformation. (a) This represents a staging PET/CT scan, the blue shaded area represents the gross tumour volume (GTV) as delineated on CT and the red outline the internal target volume as delineated on PET. The GTV on CT has been imaged at an extreme of respiration. In (b) for the same patient representing the situation in a planning PET/CT scan, the GTV on the CT has been imaged at the other extreme of respiration. (c) The staging PET/CT is undergoing deformable registration (orange lines represent direction of warp) to the planning PET/CT scan (d). As the deformation is CT based the algorithm attempts to correct for the differences in the CT components for the two scans, the subsequent deformation of the PET internal target volume (green contour) is incorrect and positioned superiorly to the PET internal target volume on the planning scan.

motion, this is not the case in the thorax. In most PET/CT acquisition protocols, the CT scan is acquired as a fast ''snap-shot'' image, imaging the entire thorax in seconds. No special breathing instructions were used and no respiratory monitoring was used. Hence, as suggested by the clinical example in Figure 4, the CT component of the staging and RTP PET/CT scans may be acquired at different phases of the respiratory cycle. By contrast, the PET component of the PET/CT scan, depending on the type of scanner and the protocol used, is usually acquired over 2–5 min for each table position. Hence the PET component of the scan contains an element of the respiratory motion of a lung tumour. It has been suggested that this four-dimensional (4D) element of a PET scan might be able to define an internal target volume, compensating for all respiratory motion [16, 23]. Thus, with current scanning protocols, a 3D scanning modality (CT) is in effect being combined with a 4D scanning modality (PET). Hence, if the respiratory phase relationship of the CT scan acquired at the staging scan is not identical to that obtained from the planning scan, then deformation of the PET-based contours, using the CT deformation map, may lead to a reduced spatial correlation as illustrated in Figure 5.

To avoid both the pitfalls of registration between scan sets and the need to acquire both staging and RTP PET/CT scans, some authors have shown that acquiring a single PET/CT scan in the radiotherapy treatment position both for the purposes of baseline staging and for the purposes of simulation may be appropriate [24]. One potential limitation of this approach is that further staging investigations, such as a mediastinal lymph node biopsy, may be required as a result of findings from the combined purpose PET/CT scan and this may introduce delay between the acquisition of the RTP PET/CT scan and commencement of treatment. Furthermore, many patients referred for radiation therapy will already have had baseline PET/CT scanning prior to referral for radiotherapy.

If registration of a staging PET scan is to be used as a means of incorporating PET in RTP simulation, one potential solution to overcome this issue is acquisition of the CT imaging with 4D information and subsequent registration of the staging PET scan to the 4D CT scan. Grgic et al [8] demonstrated that rigid registration between staging PET and RTP CT was most optimal when the RTP CT was acquired in the mid-ventilation phase of the respiratory cycle. This is intuitive, as the mid-ventilation position will have the least average position displacement when comparing the RTP CT with the staging imaging. However, for registration of a staging PET scan to a 3D RTP simulation CT scan, given the findings of this investigation, the use of rigid registration is recommended.

Conclusion

Although deformable registration improves the accuracy of CT-based registration between scan sets acquired on the same patient, transfer of contours from a staging PET scan to a standard 3D radiotherapy planning CT scan using the same deformation warp does not provide consistent improved registration. We recommend that, if conventional 3D PET/CT scan is to be used for CT simulation purposes in NSCLC, it is best performed as a dedicated radiotherapy planning scan with the patient positioned in the treatment position. If this is not possible and a staging PET/CT scan is to be registered to a non-respiration correlated 3D radiotherapy planning CT scan, then rigid registration should be used to transfer contours as best possible.

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