Introduction

Currently in the UK, oesophageal cancer has a high mortality rate with an estimated 5-year survival rate of 15% [1]. Many patients with locally advanced oesophageal cancer are treated with chemo-radiation. A large percentage of these patients will experience local recurrence within the first two years post-treatment [2,3]. Some studies suggest that persistent disease may be a result of inaccurate GTV delineation [4]. Consequently, accurate detection and delineation of the extent of disease is important. Improving this definition of the gross tumour volume (GTV) remains a challenge in oesophageal cancer [5,6].

The role of fluoride-18 fluorodeoxyglucose (FDG) positron emission tomography - computed tomography (PET-CT) imaging has been explored in recent years, with applications including tumour staging, target delineation and assessment of tumour response to treatment [7,8]. PET-CT can assist in identifying the metabolically active tumour but there remains uncertainty in how this information should be used [9-12]. Some studies suggest PET-CT may enable more accurate tumour delineation, compared to CT alone [6, 9, 13]. There are many difficulties in integrating PET-CT to the treatment planning process; primarily because the staging PET-CT is typically acquired prior to a decision to proceed with non-surgical treatment. Consequently these scans are not acquired in a radiotherapy treatment position. An additional PET-CT scan in the treatment position could be acquired but is resource intensive, onerous for patients and results in an increased radiation dose. Alternatively, the diagnostic PET-CT could be incorporated into the planning pathway using image co-registration, but the accuracy of this co-registration process is essential. Rigid co-registration in a region of interest may be suboptimal due to positional differences between the PET-CT and planning CT (pCT). Deformable image registration (DIR) provides an alternative option. It has many applications in radiotherapy treatment planning including calculating accumulative dose over a radiotherapy treatment course, and auto-segmentation for target/organ at risk delineation/to account for contour changes in adaptive radiotherapy [14-21].

Analysis of the pattern of local recurrence is critical in evaluating the quality of the radiotherapy treatment. DIR has been used for this purpose in head and neck cancer [22-24]. It represents a promising method to evaluate local recurrence and to determine whether these recurrences are within the original treatment planning volume. DIR can be used to examine the pattern of recurrence relative to the metabolically active PET-CT volume, to determine whether this represents a potential target for dose escalation strategies.

This study aims to quantify the accuracy of co-registration of diagnostic PET-CT and relapse imaging to the pCT, using both DIR and rigid registration, and to correlate the site of local recurrence with pre-treatment PET avidity.

METHODS AND MATERIALS

Patients

Data was collected retrospectively for 10 patients with oesophageal cancer who were treated between February 2009 and August 2010 with a combination of chemotherapy and external beam radiotherapy. 6 of these patients later experienced local recurrence.

Imaging

As part of routine clinical staging, all patients underwent an FDG PET-CT scan (Discovery ST, GE Medical Systems, Milwaukee, Wisconsin) an average of six weeks prior to treatment commencing (range 4-137 days). Patients were scanned on a curved couch-top with arms raised. Images were acquired from skull base to upper thigh, 60 minutes after a 400MBq dose of intravenous fluorine-18 FDG. The CT component of the PET-CT was performed according to a standardized protocol with the following settings: 140 kV; 80 mAs; tube rotation time 0.5 s per rotation; pitch 6; section thickness 3.75 mm (to match the PET section thickness). Patients maintained normal shallow respiration during the CT acquisition. No iodinated contrast material was administered. No immobilisation equipment was used.

A CT scan for treatment planning was acquired with a 24 or 40 slice, wide-bore scanner equipped with a flat couch-top (Somatom Sensation, Siemens Medical Systems, Erlangen, Germany). Patients were scanned in the supine position immobilised on a wing-board with their arms above their heads. One patient was scanned with their arms down and immobilised in a 5-point thermoplastic mask. Intravenous contrast was administered and 5mm slices were acquired from lung apices to iliac crests.

Recurrence imaging was acquired according to standard diagnostic CT protocols. Patients were scanned on a standard curved couch-top and no immobilisation equipment was used.

Radiotherapy Treatment Planning

All patients were treated according to the NCRI UK SCOPE1 trial protocol [25] and received a conformal radiotherapy treatment of 50Gy in 25 treatment fractions to the planning target volume (PTV_{TP}). The PTV_{TP} was derived from a GTV_{TP} contoured on the pCT using visual cross-reference with the unregistered FDG PET-CT scan and the endoscopic ultrasound (EUS). The GTV_{TP} was extended 2cm superiorly and inferiorly along the length of the oesophagus, and 1cm in all other directions to form a CTV_{TP}. Finally the PTV_{TP} was derived from the CTV_{TP} plus a margin of 1cm superiorly and inferiorly, and 0.5cm in all other directions.

Treatment planning was carried out using the Xio (version 4.4) treatment planning system (Elekta CMS, Stockholm, Sweden) and a 3D conformal treatment technique with 6MV beams including an anterior and posterior field and two lateral fields angled away from the spinal cord. Each plan aimed to cover 95% of the PTV_{TP} with 99% of the prescribed dose [25].

Deformable and Rigid Image Co-registration

All DIR and rigid registrations were performed using Mirada (version 1.4, RTx, Mirada Medical, Oxford, UK). The DIR algorithm was evaluated in previous work [26]. For all 10 patients, the DIR was performed over the whole image and qualitatively evaluated by a

physicist and radiation oncologist. Rigid registrations were carried out by performing an initial manual co-registration followed by a local, automatic rigid registration within a region of interest defined by the GTV_{TP} plus a 5cm margin in the superior/inferior and lateral directions and 8cm in the anterior/posterior direction. This region of interest was defined to allow the inclusion of sufficient anatomical landmarks to facilitate co-registration but to minimise the influence of positional differences distant from the GTV_{TP}.

Validation of Registration

For each patient, the accuracy of the DIR, compared to rigid registration, was qualitatively reviewed by a radiation oncologist and physicist team blinded to method of co-registration. A visual assessment was carried out looking at the coincidence of anatomical landmarks including oesophagus, trachea and aorta. The local deformation was evaluated by visually examining the deformation grid. Co-registrations were classified as clinically acceptable or unacceptable, and preference for which registration was considered superior was documented.

A quantitative assessment was performed to evaluate the accuracy of co-registration. It involved comparing outlines of the trachea (from sternal notch to carina), oesophagus (from level of sternal notch to gastro-oesophageal junction) and descending aorta (from level of sternal notch to level of gastro-oesophageal junction) on the PET-CT, pCT and relapse CT. Structures were then transferred from the PET-CT and relapse CT to the pCT, via rigid registration and DIR. Four positional metrics were calculated using ImSimQA software (v3.1.5, OSL, Shrewsbury, UK); conformity index (CI); dice similarity coefficient (DSC); sensitivity index (SI); and inclusion index (Incl). The DSC is described as the size of the union of two datasets divided by the average size of the datasets. Values range from 0 to 1 with 0 describing structure with no overlap and 1 describing structures that overlap completely. The CI is defined as the ratio of the overlapping region of two structures to the total area covered by both structures. The Incl describes the probability that a voxel of one structure is really a voxel of a reference structure. The SI describes the probability that one structure matches a reference structure and can be referred to as the overlapping index.

$$DSC = \frac{2(V_{ref} \cap V_{eval})}{V_{ref} + V_{eval}} \quad CI = \frac{V_{ref} \cap V_{eval}}{V_{ref} \cup V_{eval}} \quad InI = \frac{V_{ref} \cap V_{eval}}{V_{eval}} \quad SI = \frac{V_{ref} \cap V_{eval}}{V_{ref}}$$

Note that V_{ref} is the volume/area of a reference structure (in this case, the structure contours on the pCT) and V_{eval} is the volume/area of the structure to be evaluated (i.e. the structure contoured on the PET-CT and relapse CT).

DIR in deriving a PET-CT based GTV

Following the co-registration feasibility investigation, DIR was used to derive a GTV using a combination of PET-CT and pCT. For all 10 patients, the metabolically active volumes were contoured by a physicist on the PET-CT images, using 50% of maximum SUV thresholding. Volumes were reviewed by a dual-certified nuclear medicine physician and radiologist, and contours edited manually if required. Structures were transferred to the pCT using DIR. Contours were reviewed by a radiation oncologist and the entire circumference of the

involved oesophagus, as determined by the PET-CT, was outlined to define the GTV (GTV_{PET-CT}). This volume was grown according to the clinical protocol to produce a PET-CT derived PTV (PTV_{PET-CT}). For 6 patients who experienced local recurrence, the relapse volume ($GTV_{relapse}$) was contoured on the diagnostic relapse CT. DIR was used to transfer this volume to the pCT where, if required, it was edited by a radiation oncologist.

Comparison of Volumes

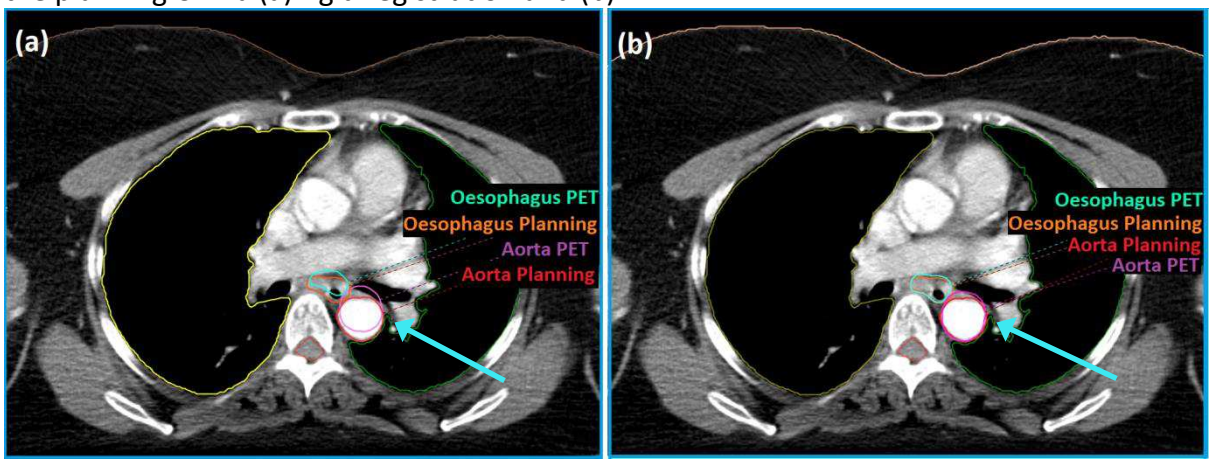
For each patient, both the volume and lengths of the GTV_{PET-CT} and PTV_{PET-CT} structures were compared to the original treatment planning structures (GTV_{TP} and PTV_{TP}). A visual comparison of the location of the relapse volumes ($GTV_{relapse}$), relative to both the PTV_{PET-CT} and PTV_{TP}, determined whether the site of relapse was contained within these structures. The Incl was used to examine whether any correlation exists between $GTV_{relapse}$ and the PET-avid volume. Dosimetric analysis was carried out by measuring the V95%, i.e. the volume receiving 95% of the prescribed treatment dose, of each structure to assess coverage.

RESULTS

Qualitative Assessment of Registration

All co-registrations of PET-CT to pCT were considered clinically acceptable; DIR was rated as superior to rigid registration for all 10 patients and the preferred method for registration. A representative example is shown in Figure 1. The co-registration of the relapse CT to pCT was considered acceptable for five of six patients. For one patient, co-registration was not possible as the patient had had a stent inserted into the oesophagus at the time of the relapse CT. This resulted in large variations to the position of the trachea and aorta compared to the pCT.

Figure 1
A visual examination of the oesophagus and aorta structures mapped from the PET-CT to the planning CT via (a) rigid registration and (b) DIR.



Quantitative Assessment of Registration

The positional metrics analysis of co-registration of the PET-CT to the pCT are summarised in table 1. DIR was significantly superior to rigid registration for multiple metrics, as shown. A non-significant trend towards superiority of DIR was observed across all metrics for all structures.

For all patients, a volumetric comparison of the metabolically active tumour volumes, before and after DIR, was used to examine the local deformation and ensure that the deformation algorithm conserved volume in these regions. An average absolute difference in volume of 1.3cm^3 (range -5 to 6.7cm^3) was observed, with a maximum increase in volume of 6.7cm^3 for one patient (48.9cm^3 on PET-CT to 55.6cm^3 on planning CT).

Quantitative analysis of co-registration of relapse CT to pCT was performed for the five patients for whom co-registration had been deemed clinically acceptable. Table 2 summarises these results, showing superiority of DIR for multiple metrics, with a trend towards DIR being superior to rigid registration for all positional metrics and all structures.

Table 1
Quantitative evaluation of DIR and rigid registration between PET-CT and pCT using positional metrics

Structure	Registration	PET CT to Planning CT (n=10)			
		CI	**DSC**	**InclI**	**SI**
Oesophagus	DIR	0.61	0.77	0.84	0.72
	Rigid	0.53	0.70	0.73	0.68
	p-value	*0.17*	*0.16*	*0.04*	*0.60*
Trachea	DIR	0.79	0.88	0.94	0.84
	Rigid	0.57	0.70	0.70	0.70
	p-value	*0.002*	*0.01*	*0.002*	*0.08*
Descending Aorta	DIR	0.86	0.93	0.92	0.95
	Rigid	0.78	0.88	0.88	0.88
	p-value	*0.04*	*0.03*	*0.15*	*0.01*

Table 2
Quantitative evaluation of DIR and rigid registration between relapse CT and pCT using positional metrics

Structure	Registration	Relapse CT to Planning CT (n=6)			
		CI	**DSC**	**InclI**	**SI**
Oesophagus	DIR	0.61	0.74	0.87	0.65
	Rigid	0.37	0.51	0.59	0.45
	p-value	*0.06*	*0.08*	*0.03*	*0.10*
Trachea	DIR	0.83	0.91	0.93	0.90
	Rigid	0.51	0.66	0.63	0.70
	p-value	*0.00*	*0.01*	*0.00*	*0.05*
Descending Aorta	DIR	0.83	0.91	0.9	0.93

	Rigid	0.63	0.75	0.76	0.73
	p-value	*0.06*	*0.06*	*0.10*	*0.04*

PET-based GTV and PTV delineation

Table 3 shows the length and volume of GTV and PTVs. Median GTV_{PET-CT} and GTV_{TP} lengths were 4cm (range 0.5-7cm) and 7cm (range 3.5-10.5cm) ($p<0.003$) respectively. Median PTV_{PET-CT} and PTV_{TP} lengths were 10cm (range 6-13cm) and 13.5cm (range 9.5-16cm) ($p<0.003$). A mean reduction of 1.7cm (0.5 to -4cm) was observed in the superior direction while the inferior extension had a mean reduction of 1.4cm (3 to -4cm).

Table 3

A comparison of PTV length and PTV volume for PET-CT derived and treatment planning CT derived structures.

Patient	Length (cm)				Volume (cm^3)			
	GTV_{PET-CT}	PTV_{PET-CT}	GTV_{TP}	PTV_{TP}	GTV_{PET-CT}	PTV_{PET-CT}	GTV_{TP}	PTV_{TP}
1	6.5	12.5	6.5	14	39.4	318.8	51.5	371.5
2	0.5	6.5	3.5	9.5	2.6	129.5	9.4	310.6
3	5	11	8	14	33.5	305.7	45.3	295.9
4	4	10	6.5	16	18.3	246.1	20.6	415
5	3	9	9	15	13.1	204.8	31.3	388.1
6	7	13	9	15	36.8	361.6	48.4	454.9
7	4	10	7	13.5	20.3	241.5	34.7	247.7
8	2	8	7	12	10.5	220.5	33.7	251.3
9	5	11	5	11	96.4	493.6	42	457.4
10	2	8	3.5	9.5	5	149.5	6.7	140.6

Note: Patients 1-6 represent the relapse patients.

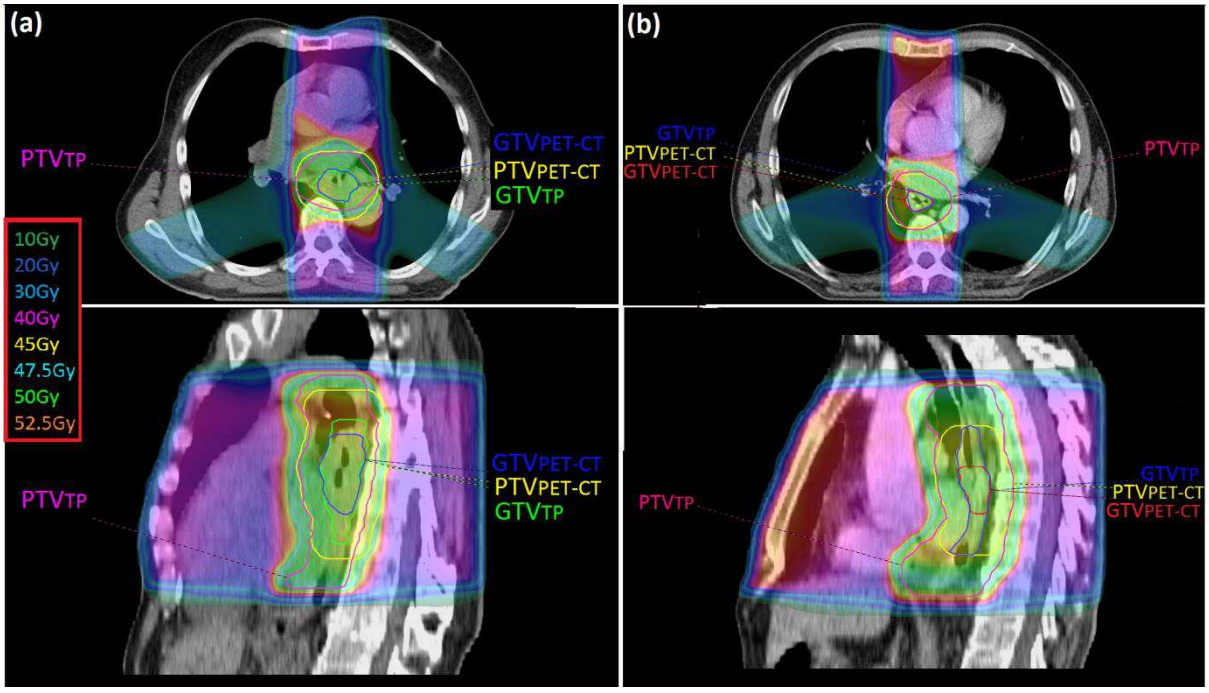


Figure 2: Examples of the location of GTV_{TP}, PTV_{TP}, $GTV_{PET\text{-}CT}$ and $PTV_{PET\text{-}CT}$ relative to the high dose region; (a) For patient 3, the $PTV_{PET\text{-}CT}$ extends posteriorly compared to PTV_{TP} but is still contained within the high dose region (b) For patient 5, both the $GTV_{PET\text{-}CT}$ and $PTV_{PET\text{-}CT}$ are contained within the high dose region.

A comparison of the positions of GTVs and PTVs, relative to the high dose region (i.e. the volume covered by 95% of the prescribed treatment dose) can be observed for two patients in figure 2.

Relapse Patients

Dosimetric analysis was also performed to assess the coverage of $GTV_{relapse}$ structures, relative to the $PTV_{PET\text{-}CT}$ and PTV_{TP} structures. Patient 2 was omitted due to a stent inserted in the oesophagus prior to the relapse CT, which meant image co-registration was not possible. Dosimetric analysis showed that, with the exception of patient 2, 100% of the relapse volumes were contained within the V95%. The InclI was used to examine whether any correlation exists between the location of the relapse volume and the $GTV_{PET\text{-}CT}$ and $PTV_{PET\text{-}CT}$. Results are summarised in table 4.

Table 4
The InclI looks at the probability that a voxel of $GTV_{relapse}$ is contained within $GTV_{PET\text{-}CT}$ and $PTV_{PET\text{-}CT}$

Patient	Inclusiveness Index		
	$GTV_{relapse}$ to $GTV_{PET\text{-}CT}$	$GTV_{relapse}$ to $CTV_{PET\text{-}CT}$	$GTV_{relapse}$ to $PTV_{PET\text{-}CT}$
1	0.69	0.99	1
2	*	*	*
3	0.84	1	1
4	0.6	0.85	0.94
5	0.45	0.88	1
6	0.7	0.93	1

*Omitted due to oesophageal stent insertion.

DISCUSSION

The benefits of the integration of PET-CT into the planning process have been widely discussed [27-30]. However, this process is challenging, mainly due to the variations in patient setup between diagnostic and planning scans. The availability of a dedicated planning PET-CT for oesophageal carcinoma is not widely accessible. Therefore, the use of image co-registration to facilitate this integration is highly relevant. This is in view of the importance of improving the quality of GTV delineation in order to avoid a geographic miss. It can also assist in identifying a suitable target for future dose escalation studies. This study shows that image co-registration offers a suitable method of incorporating diagnostic PET-CT imaging to the treatment planning process.

There is no definitive method of validating the accuracy of a registration but fixed landmark placement and ROI-based comparisons have been used [31-32]. This study applied an ROI-

based method of validation, choosing structures which were easy to identify and contour, and adjacent to the treatment field. Both qualitative and quantitative analysis showed that DIR was superior to rigid registration in accurately registering diagnostic PET-CT and relapse CT imaging to a pCT. Co-registration using DIR was significantly superior by multiple positional metrics, with a non-significant trend to superiority in all comparisons. Importantly, blinded clinical qualitative assessment found that the co-registration of PET-CT to pCT was clinically acceptable for planning purposes and superior with DIR. The difference between DIR and rigid registrations was more pronounced in the relapse CT to pCT registrations. This is perhaps unsurprising as a significant period of time has passed between scans; relapse CT scans were acquired an average of 11 months after the planning CT (range of 4-17 months) compared to PET-CT scans which were acquired an average of 1.5 months prior to treatment commencing (range of 0.1-4.5 months). Therefore large changes to external anatomy in this time-frame are expected. Despite this, visual assessment of the DIR by a clinical oncologist and physicist team found them to be clinically acceptable for all but one patient who had an oesophageal stent inserted.

Results showed that using t PET-CT registered to pCT to derive a GTV will result in a shorter PTV length than contouring according to the current clinical protocol. Results also show a median reduction in superior PTV length of 1.7cm and a median reduction in the inferior PTV length of 1.4cm when using registered PET-CT in conjunction with the planning CT. This data is consistent with several previous studies which have shown that the addition of PET imaging leads to a reduction in PTV length [6, 9, 33] and volume [34].

This study used DIR to analyse the pattern of recurrence for a group of patients, to determine whether any correlation exists between the site of these recurrences and the $PTV_{PET\text{-}CT}$. This has previously been examined for head and neck patients [35]. Local recurrences were classified as 'infield', 'marginal' or 'out-of-field' if more than 95%, 20-94% and less than 20% of the recurrence volume was within the 95% isodose line [23]. Dosimetric analysis for the 5 relapse patients studied showed that all relapse volumes were in the high dose treatment field within both the $PTV_{PET\text{-}CT}$ and PTV_{TP}. This is supported by previous work which examined the pattern of local recurrence and found that the majority of recurrences occurred within the treatment field [2]. The InclI was also used to determine whether this recurrence volume was contained within $PTV_{PET\text{-}CT}$ and PTV_{TP} structures. An average InclI of 0.66 (range of 0.45-0.84) suggests some degree of correlation between the relapse volumes and the $GTV_{PET\text{-}CT}$. A large correlation exists between the relapse volumes and $CTV_{PET\text{-}CT}$ with an average InclI of 0.93 (range of 0.85-1). This preliminary data suggests local recurrences are predominantly due to resistant disease rather than a geometric miss. Dose escalation using a synchronous boost may be necessary to reduce this likelihood of treatment failure. The suggested correlation between the relapse volumes and $CTV_{PET\text{-}CT}$ suggests that the metabolically active PET volume, plus a margin, could be used as a target in dose escalation studies. These findings support the planned UK SCOPE2 trial where dose escalation using a synchronous boost will be used, although the sample size is small.

Limitations

There are several limitations to this study. The patient sample is small and further investigation using a larger patient cohort is required to verify these results. There is also a

lack of a validated method of GTV delineation using PET-CT, including the optimum SUV maximum threshold for delineating the metabolically active volume on the PET-CT [10-13]. A prior study focusing on cervical cancer showed that the minimum threshold representing tumour volume was 40% of maximum SUV with values less than this included additional background uptake [36]. An additional study reported that values of greater than 80% SUV max should be avoided as tumour volumes are small and the partial volume effect is pronounced [37]. Consequently, this study uses a pragmatically determined value of 50% of maximum SUV thresholding. This reflects a compromise between the two and the cut off used by diagnostic PET radiologists when reporting on the length of the tumour. Therefore 50% of maximum SUV represented current clinical practice.

This study has shown, through both quantitative and qualitative analysis, that DIR allows more accurate image co-registration than rigid registration for both PET-CT and relapse CT to pCT registration. However, the time interval between the pCT and PET-CT and, in particular, the relapse CT, means that significant changes to patient anatomy (e.g. weight loss) and tumour volume may have occurred. This can result in inaccuracies in the image co-registration. This was observed for one patient where an oesophageal stent had been inserted prior to acquisition of the relapse CT. A detailed check of image registration should be carried out prior to the transfer of PET-CT and relapse volumes to the pCT. This time interval is of critical importance in deciding whether it is appropriate to use a diagnostic PET-CT in the radiotherapy planning process; the potential for tumour progression in the intervening period needs to be considered.

CONCLUSION

DIR is superior to rigid registration and represents a feasible and practical approach for integrating PET-CT imaging to the treatment planning process for oesophageal radiotherapy. Using DIR to examine the pattern of relapse is a valuable tool in assessing the quality of radiotherapy treatment. It enables comparison of relapse CT data with pCT data to determine whether current target delineation is appropriate. Analysis of the pattern of local recurrence for five patients suggests geometric miss of the volume due to the initial treatment planning was unlikely, and treatment intensification using a synchronous boost could have clinical benefits; a metabolic, biological tumour volume derived from the PET-CT represents a potential target.

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