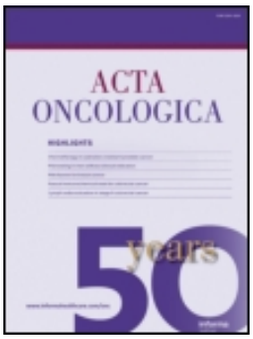

Acta Oncologica

ISSN: 0284-186X (Print) 1651-226X (Online) Journal homepage: informahealthcare.com/journals/ionc20

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To cite this article: Maria A. Hawkins, Alexandra Aitken, Vibeke N. Hansen, Helen A. McNair & Diana M. Tait (2011) Cone beam CT verification for oesophageal cancer – impact of volume selected for image registration, Acta Oncologica, 50:8, 1183-1190, DOI: 10.3109/0284186X.2011.572912

To link to this article: https://doi.org/10.3109/0284186X.2011.572912

Acta Oncologica, 2011; 50: 1183–1190

informa
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ORIGINAL ARTICLE

Cone beam CT verification for oesophageal cancer – impact of volume selected for image registration

MARIA A. HAWKINS[1], ALEXANDRA AITKEN[1], VIBEKE N. HANSEN[2], HELEN A. McNAIR[1] & DIANA M. TAIT[1]

[1]*Department of Radiotherapy, The Royal Marsden Hospital NHS Foundation Trust, Sutton, Surrey SM2 5PT, UK, and* [2]*Joint Department of Physics and Radiotherapy, Royal Marsden NHS Foundation Trust and Institute of Cancer Research, Sutton, Surrey, UK*

Abstract

Purpose. Oesophageal cancers are difficult to visualise on volumetric imaging and reliable surrogate are needed for accurate tumour registration. The aim of this investigation is to evaluate the effect of a user defined volume with automated registration techniques using commercially available software with the on-board volumetric imaging for treatment verification of oesophageal cancer and determine the optimum location of this volume. *Material and methods*. In 20 patients four 'clipbox'(C) volumes were defined: C-planning target volume (PTV), C-carina, C-vertebrae, C-thorax. The set-up corrections (translational and rotational) for C-PTV were compared to the corrections using C-carina, C-vertebrae and C-thorax. *Results*. Six hundred and eight registrations were performed. The best concordance in set-up corrections was found in the superior/inferior direction between C-PTV and C-carina (76%). In the right/left and anterior/posterior direction, better agreement was found between C-PTV and C-thorax with 80% and 76% agreement, respectively. Automatic 'bone' registration using C-vertebrae failed in 28% of scans. The correlation ratio between C-PTV and C-carina (n = 4) for mid-oesophageal tumours was 0.88, 0.79, and 0.95 in the right/left, superior/inferior and anterior/posterior directions, respectively. *Conclusion*. The defined volume for matching is important for oesophageal tumours. The alignment 'clipbox' and registration method selected can affect the displacements obtained. This may best be determined by tumour location and highlights the need to diversify protocols within one tumour treatment site. Further analysis is required to validate carina as a tumour surrogate for mid-oesophageal tumours.

The current standard treatment for squamous carcinoma and locally advanced or inoperable adenocarcinona of the oesophagus is chemoradiation [1,2]. Technical advances in radiotherapy have assisted with target definition and volumetric assessment of dose received by normal tissues, thereby offering the possibility to decrease toxicity associated with radiotherapy due to possible reduction in target volumes and increased conformity of radiotherapy [3,4].

The oesophagus is a mobile structure and tumours in the distal oesophagus can prove particularly difficult to identify on diagnostic/planning computed tomography (CT)-scans. Currently image co registration with positron emission tomography (PET) is becoming the standard for gross tumour volume (GTV) delineation [5,6]. Two dimensional (2D) megavoltage (MV) portal imaging is commonly used to verify radiotherapy delivery for oesophageal tumours; however the poor soft tissue detail obtained in these images makes this difficult. Consequently, bony anatomy is used as a surrogate to verify treatment position and by extrapolation confirm tumour location. Endoscopically inserted clips are not routinely used as they are not a reliable surrogate marker for tumour site as they are frequently displaced within days of being implanted.

Tumour motion is included in the radiotherapy planning of upper gastro-intestinal tumours and in order to minimise geographic miss, the planning target volume (PTV) has to account for set-up variations and both interfraction and intrafraction target motion and position. To include the intrafractional

Correspondence: Maria A. Hawkins, Royal Marsden Hospital NHS Foundation Trust, Sutton, Surrey SM2 5PT, UK. Tel: +44 2086613365. Fax: +44 2086613160. E-mail: maria.hawkins@rmh.nhs.uk

(Received 11 January 2011; accepted 12 March 2011)

ISSN 0284-186X print/ISSN 1651-226X online © 2011 Informa Healthcare
DOI: 10.3109/0284186X.2011.572912

respiratory motion, a large volumetric expansion of the clinical target volume (CTV) is generally applied [7]. Tumours of the gastro-oesophageal junction can exhibit considerable respiratory induced motion therefore methods to quantify oesophageal motion should be contemplated for radiotherapy planning [8,9]. A free breathing CT-scan can be used for radiotherapy planning if adequate margins for motion and set-up are incorporated in the PTV definition [10]. There is still a risk of geometric miss if tumour motion is greater than the assumed average motion, and conversely there may be unnecessary normal tissue irradiation if the tumour motion is smaller than expected. Image guided radiotherapy can aid in quantifying and addressing soft tissue set-up and kilovoltage cone beam CT (kVCBCT) is becoming more commonly used for treatment verification. kVCBCT provides detailed three dimensional (3D) soft-tissue and bone information facilitating accurate verification [11–13]. Accurate treatment delivery is essential to enable a reduction in PTV margins and allow dose escalation. Despite the availability of new technology, oesophageal tumours remain challenging to visualise and reliable surrogates are required for accurate tumour registration.

The current on board volumetric imaging software offers the option of defining an individualised 'Region of Interest' or 'clipbox', which demarcates the volume over which the automatic image registration is to be performed. Currently there are no published strategies on the region of interest size/volume or anatomical structures that should be incorporated when defining this volume, and which automatic matching algorithm to use, for verification of oesophageal tumours. The available training guides' state that it is a clinical decision to determine the position and size of the region of interest with regards to specific anatomical sites and protocols, as results may change depending on the dimensions and location of the clipbox. Different techniques of rigid registration are practicable such as grey scale or bone registration or grey scale followed by bone registration and these have been described in literature [14]. Furthermore, to confound the matter further, the field of interest or clipbox varies even for the same tumour site, depending on the investigators [15–17] and lung cancer studies exploring direct tumour registration have shown poor correlation between bony anatomy and the tumour position [18,19]. When the patient specific volume was defined as the PTV contour with a margin we have demonstrated that CBCT verification offers adequate 3D volumetric image quality [13] to improve the accuracy of treatment delivery for the radiotherapy of oesophageal cancers.

This study investigates the effect of using different 'clipbox' volumes in the image registration (or anatomy match) for image guided radiotherapy (IGRT) of oesophagus cancer in order to determine the optimum volume for soft tissue match.

Methods and materials

Patients' characteristics and planning

An ethics approved prospective study (CCR ref: 2867, REC reference:06/Q0801/164) was carried out on patients diagnosed with histologically confirmed adenocarcinoma or squamous cell carcinoma of the oesophagus that received radical radiotherapy (patient characteristics are summarised in Table I). All patients were immobilised using an in-house developed lung board and commercial knee support – Kneefix (Sinmed Radiotherapy Products, Reeuwijk, The Netherlands). A free breathing helical CT-scan (reconstruction slice thickness of 2.5 mm) was performed in the treatment position and was used as the reference scan for image registration with the CBCT. The GTV included the tumour and involved lymph nodes as defined by diagnostic CT esophagogastroscopy, endoscopic ultrasound, and PET scan. The CTV included the GTV and an extension in the cranio-caudal direction along oesophagus between 3 cm and 5 cm to include microscopic spread. The PTV was defined by adding 1.0 cm margin three dimensionally to the CTV to create ITV and to the ITV a set-up error of 0.5 cm three dimensionally to create PTV. These margins were applied for all oesophageal tumour and was the departmental protocol at the time. A treatment plan was then created with the isocentre situated near the geometrical centre of the PTV.

CBCT imaging

The Elekta Synergy XVI system (version 3.5/4.0., Elekta Oncology Systems Ltd Crawley, West Sussex,

Table I. Patients characteristics.

No. of patients	20
Male/female	14 Male 6 Female
Age mean (range)	66 (41–84)
Pathology	12 Adenocarcinoma 8 Squamous cell carcinoma
Stage (AJCC)	1 = I 4 = IIa 5 = III
Total dose delivered/fractions	54 Gy in 30# (18) 60 Gy in 30# (2)
Tumour location	4 thoracic (mid) 5 lower 11 gastro-oesophageal junction
GTV length cm mean (range)	5.4 cm (3–7 cm)

England) was used to acquire CBCT scans of the patients in treatment position prior to radiation delivery. The following scanning protocol was used: approximately 650 2D kV images were acquired during a two minute, 360 degree rotation with the patient immobilised in the treatment position. The acquisition parameters were 120 kV, 25 mA, 40 ms per projection (with clinical filter F0). From October 2007 the acquisition parameters were 120 kV, 40 mA and 40 ms (with clinical filter F1), maintaining the dose to the patient but improving image quality. Commissioning and calibration of the CBCT isocentre to the linear accelerator isocentre was performed prior to initiation of this study according to recommended guidance [20,21].

M20 collimator cassette was used on all patients giving a nominal irradiated scan length at the isocentre of approximately 26 cm and reconstruction diametre of approximately 40 cm (Elekta Synergy, Clinical User manual for XVI R3.5). The 3D CBCT scan was reconstructed using a reconstruction process based on the Feldkamp-Davis-Kress (FDK) algorithm using medium resolution [22].

CBCT scans were acquired fractions 1–3 and weekly thereafter. The planning CT-scan was imported into the XVI database via DICOM. A patient specific volume ('clipbox') was defined around the PTV, on the reference CT, and an automatic 'grey value' match was used for treatment verification purposes. This is the current institutional standard following implementation of cone beam CT for treatment verification. The correction reference point was set to the isocentre. A no action level protocol was used and corrections were made for any systematic errors greater than 2 mm. An additional scan was acquired to confirm any systematic corrections made.

Volume of interest / 'Clipbox' definition

Four image registration techniques were evaluated retrospectively off line using the automatic matching algorithms. 'Clipbox'(C) volumes were defined as: C-PTV, C-carina, C-vertebrae and C-thorax (Figure 1a, b, c and d). C-PTV represents the tumour and planning margin and encompassed the PTV contour from the planning CT plus a 3D margin of 0.5 cm. C-carina was investigating the possible use of carina as a surrogate for tumour position as this structure is easily identified on CBCT scans and could facilitate image registration. Anatomically the oesophagus is situated posterior to the carina and would be therefore included in the volume matched. This included the bifurcation of the trachea into the bronchi with a 1.0 cm margin in all directions. This volume would be a good representation of the position of the tumours situated in the mid-oesophagus and would be assessed further. C-vertebrae incorporated the vertebrae running the length of the PTV with a 1.5 cm margin circumferentially and extended to the nearest inter-vertebral space in the superior and inferior directions, this 'clipbox' would be an equivalent of the 2D MV orthogonal image verification, which is approximately 10–14 cm in length and currently used as back-up for IGRT should CBCT verification not be available. C-thorax included all the bony anatomy within the CBCT dataset. Two automated registration algorithms are available to calculate the correspondence between the CBCT and reference scan: a soft tissue (grey level correlation ratio) or bone (Chamfer matching) technique. The soft tissue registration method uses the voxel greyscale intensity values throughout the volume defined by the 'clipbox', volume while the 'bone' match uses the chamfer matching algorithm [23]. These registration techniques have been methodically tested [24–26] and are part of the software provided by the manufacturer. Higgins et al. [13] have demonstrated that automatic matching gives the highest agreement for an individual. We chose soft tissue registration for C-PTV and C-carina as we wanted to have a description of tumour position and bony registration for C-vertebra and C-thorax as whole vertebral bodies were included.

Registrations were defined as successful if the matching algorithm used was completed successfully, and if the match within the volume defined 'clipbox' was verified as acceptable by the observer by carrying out a visual check. Registrations were determined as unsuccessful if an error message was returned, and subsequently the match was aborted, or if the visual check by the observer deemed the registration incorrect. A colour scale of green (CBCT scan) and purple (planning CT scan) was used to facilitate visual interpretation of the results, sharp white borders around the structure of interest represented a successful match, and green and purple edges depicted a mismatch. No manual match was performed in this study as automatic and manual registrations performed on bone and carina have been reported as highly reliable [15]. Furthermore no additional observers were used, as the purpose of this study was not to address inter-observer variability but image registration variability when defining different regions of interest.

Translational shifts for the automated image registrations were recorded in the right/left (Rt/Lt), superior/inferior (Sup/Inf) and anterior/posterior (Ant/Post) directions in relationship to the isocentre of the planning CT. Rotational shifts for each image registration were also recorded (pitch (x), roll (y) and yaw (z)).

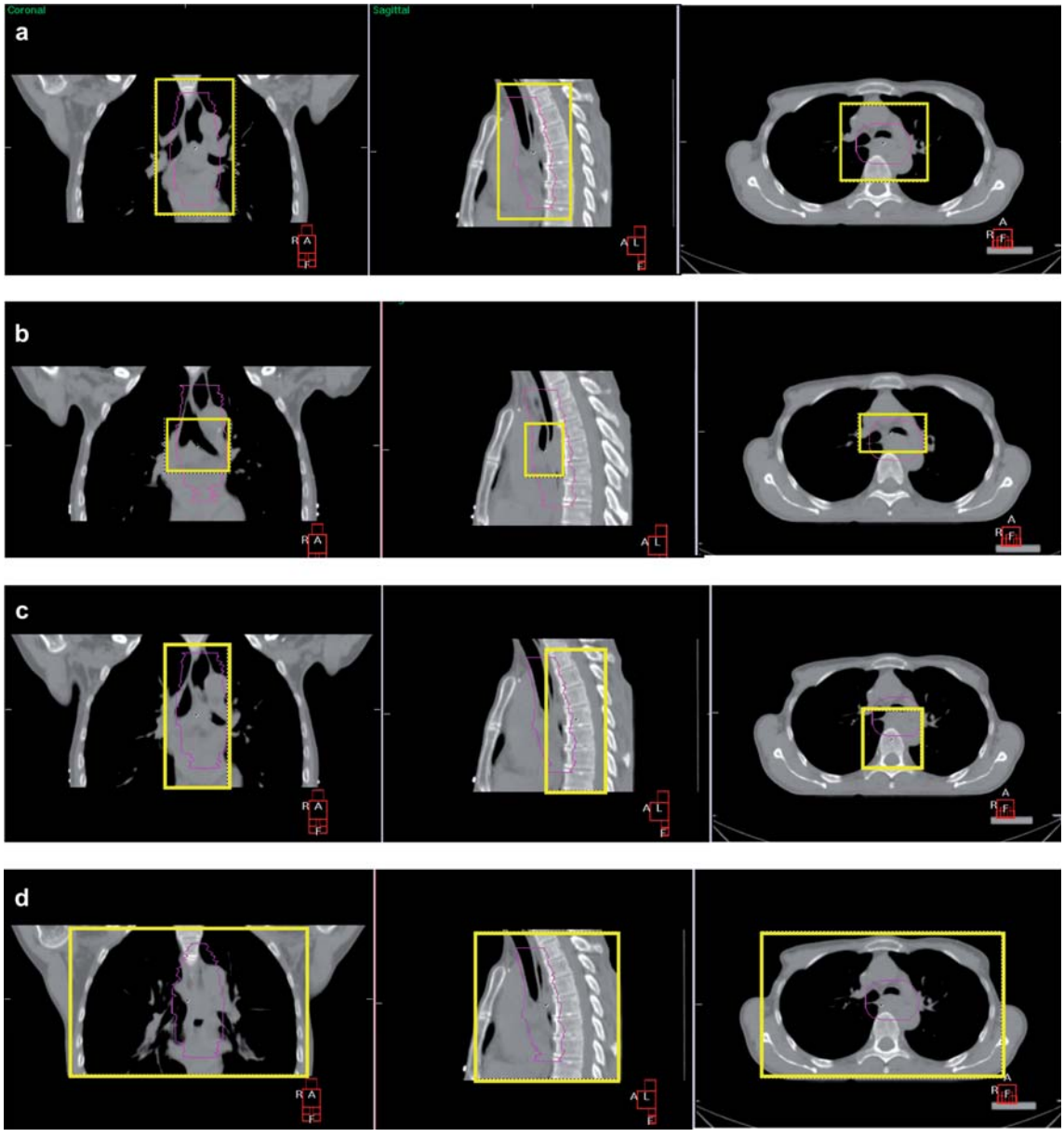

Figure 1. CT and CBCT overlay in coronal and transverse and sagital plane. The area defined in yellow represents C-PTV (a), C-carina (b), C-vertebrae (c) and C-thorax (d) clipbox definition.

The set-up errors were calculated as previously described [27,28] and systematic and random errors for each of the 'clip-boxes' were calculated. The mean and standard deviations were calculated for the translational and rotational errors for each patient. The mean value expressed the systematic error and the standard deviation describes the random error. Systematic errors greater than 2 mm were then investigated as it is current departmental protocol to correct for systematic errors greater than 2 mm. C-PTV was taken as the standard as it includes the target volume and would be a surrogate for tumour position. The relationship between C-PTV and the other 'clipbox' defined volumes was then investigated for differences greater than 2 mm for each image acquired. Agreement was defined as errors within 2 mm in the same direction. For cases with mid oesophagus tumours the relationship between C-PTV and C-carina was also investigated using the Pearson correlation coefficient.

The length of time taken for the different registration algorithms and 'clipboxes' was recorded.

Results

Between April 2007 and August 2008 20 patients were consented to the study. Each patient had CBCT scans acquired as per protocol. One patient had an

Table II. Summary of whole population average systematic and random translational errors.

	C-PTV			C-carina			C-thorax		
	Rt/Lt	Sup/Inf	Ant/Post	Rt/Lt	Sup/Inf	Ant/Post	Rt/Lt	Sup/Inf	Ant/Post
Σ (cm)	0.14	0.26	0.14	0.19	0.23	0.26	0.15	0.26	0.12
σ (cm)	0.26	0.39	0.20	0.27	0.34	0.25	0.25	0.33	0.17
Max (cm)	0.98	1.5	0.61	0.94	1.48	0.85	0.88	1.32	0.61

Σ, systematic error; σ, random error; Rt, right; Lt, left; Sup, superior; Inf, inferior; Ant, anterior; Post, posterior.

expandable metallic stent inserted prior to planning CT. One patient was not included in the analysis as a small proportion of the PTV was not encompassed in the CBCT scan, therefore the C-PTV clipbox could not be defined. The first eight CBCT scans acquired for each of the 19 patients were analysed. One hundred and fifty-two scans were registered with four different 'clipbox' positions (giving a total of 608 registrations).

C-PTV, C-carina and C-thorax were registered successfully with the automated match. When using C-vertebrae, 28% (43/152) of registrations failed completely (i.e. no solution could be found using the chamfer matching algorithm, and an error message was returned).

A summary of the systematic and random translational and rotational errors as a whole population average is presented in Tables II and III, respectively. Overall for the population, all systematic and random errors were < 4 mm and all rotational errors were < 2 degrees.

Rotations > 3 degrees were identified on 8.5% (13), 8.6% (13) and 4.6% (7) scans using C-PTV, C-carina and C-thorax, respectively.

There was poor agreement when comparing C-vertebrae registration 'clipbox' to the others, with only 47%, 38% and 17% agreement in the Rt/Lt, Sup/Inf and Ant/Post directions, respectively, when registering with C-PTV. Fifteen percent of registrations (23/152) performed using this 'clipbox' and algorithm were fused incorrectly (although no error message was given). For these reasons, we did not proceed with further analysis of C-vertebrae.

Comparison of set-up errors

The percentage of registrations within 2 mm using C-carina, C-vertebrae and C-thorax when compared to C-PTV, are depicted in Figure 2. C-vertebrae showed poor agreement with less than 50% concordance within 2 mm in all directions and this is a further reason we did not proceed with additional analysis of C-vertebrae. A better agreement in the superior/inferior direction was found when comparing C-PTV and C-carina with 76% of scans showing good agreement. Better concordance in Rt/Lt and Ant/Post direction was shown between C-PTV and C-thorax with 80% and 76% of scans showing agreement, respectively.

When rotations were investigated, there was agreement within two degrees in all directions in more than 60% of cases when C-carina was compared to C-PTV and more than 70% of cases when C-thorax was compared to C-PTV (Figure 3).

Carina correlation

Further analysis was done in order to explore whether carina may be a suitable surrogate for mid-oesophageal tumours. The correlation ratio (r) between C-PTV and C-carina ($n = 4$) for mid-oesophageal tumours was calculated (32 CBCT matched). The correlation ratio (r) was 0.88, 0.79, 0.95 in the right/left, superior/inferior and anterior/posterior directions respectively. The rotation correlation was 0.74, 0.72 and 0.89 in the pitch, roll and yaw directions. To test if carina could be a surrogate for tumours in the lower third of the oesophagus analysis was carried out on patients with lower and gastro-oesophageal tumours ($n = 15$). This showed acceptable correlation (r) in the Rt/Lt, and Sup/Inf right/left directions with 0.84 and 0.87, respectively, however the correlation in the Ant/Post direction was 0.67, however the rotation correlations were 0.42, 0.45 and 0.60 in the pitch, roll and yaw directions.

Timings

The 'bone' automated registration ranged between 5–10 seconds, and the 'grey' value automated registration ranged between 20–75 seconds (with C-PTV taking the longest time).

Table III. Summary of whole population average systematic and random rotational errors.

	C-PTV			C-carina			C-thorax		
	Pitch	Roll	Yaw	Pitch	Roll	Yaw	Pitch	Roll	Yaw
Σ (°)	1.12	1.26	1.20	1.45	1.58	1.26	0.55	1.33	1.01
σ (°)	0.97	1.19	1.23	1.14	1.47	1.13	0.56	0.98	1.01
Max (°)	4.7	9.0	6.8	5.8	6.7	4.6	2.5	4.4	4.5

Σ, systematic error; σ, random error.

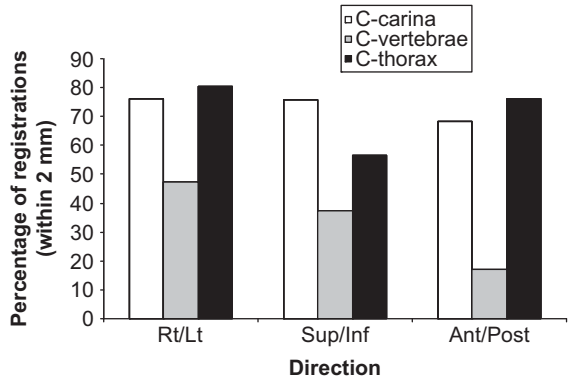

Figure 2. Percentage of registrations within 2 mm when C-carina, C-vertebrae and C-thorax compared to C-PTV clipbox.

Discussion

The use of definitive chemoradiation is the current standard of care in the management of inoperable oesophageal tumours [29]. Reducing the set-up margin for this patient group would result in a reduction of normal tissue irradiated. It is of great importance to minimise side effects as the patients are elderly and often have medical co morbidities.

The ability to use 3D target matching for treatment verification raises awareness of organ motion and changes in tumour shape and size during the course of radiotherapy. CBCT and selected areas of interest have been used clinically for IGRT of prostate cancer [30] and lung cancer [15]. Although the application of verification for oesophageal cancer is more challenging due to difficulties in tumour visualisation, automated image matching is a feasible option and offers considerably more soft tissue visualisation than 2D MV imaging [31].

In this study set-up errors were evaluated using specific volumes created on 3D CT datasets using automated image registration techniques. The set-up errors and rotations detected by all 'clipboxes' are similar to data reported by other studies [16,17]. However, using the vertebral bodies as an area of interest resulted in a significant number of failed and incorrect registrations highlighting the importance of the defined match area. The difference in set-up errors using the two automatic registration algorithms over four different volumes of interest highlights potential advantage of a patient specific 'clipbox' definition for CBCT image guided radiotherapy. It is sometimes difficult to assess PTV coverage of the oesophagus as this structure can be challenging to identify on the CBCT scans and the contrast resolution is insufficient for tumour to tumour matches, however the improved image quality does have a definite effect on informing set-up accuracy using suitable surrogates. The carina could be a good surrogate in mid oesophageal tumours but further investigation needs to be carried out due to the small number of patients in this study (n = 4). The poor correlation between C-PTV and C-carina (r = 0.67) found in the anterior/posterior direction in tumours located in the lower oesophagus and gastro-oesophageal junction (n = 15) could possibly be due to the increased distance between the carina and lower oesophagus resulting in greater differential motion between these two structures due to respiration. In addition the increased amount of artefacts in the match area (C-PTV) as a result of increased respiratory and cardiac motion could potentially affect image registration. Only few studies investigating the respiratory motion of the oesophagus have been published and the consensus is that mobility varies depending on the oesophageal location, with most motion occurring in the oesophageal junction [7–9]. Respiratory correlated cone beam CT [32–34] allows tumour motion assessment at the time of treatment and target localisation based on multiple phases of the breathing cycles, however this application is available only as a research tool and has been investigated for lung cancer [32]. Developing protocols using direct tumour matching has raised concerns regarding tumour regression during treatment [35], however this was not the case in the current study. This could be explained by the use of neoadjuvant chemotherapy for up to 12 weeks prior to radiation delivery. Patients with metallic stents in place could benefit further from this technique as the stent could be used a surrogate for tumour position; however the risk of stent migration must be taken into account especially when inserted in the gastro-oesophageal region. In addition, the presence of artefacts on the CBCT scans may have an effect on image registration results, however in the one patient analysed within this study no significant artefacts were present.

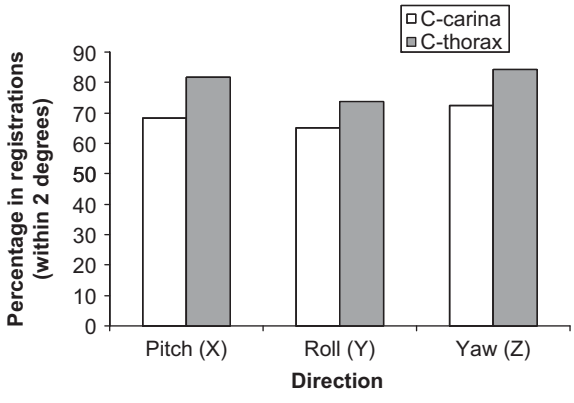

Figure 3. Percentage of rotations within 2 degrees when C-carina and C-thorax compared to C-PTV clipbox.

No inter-observer analysis was carried out in this study as only automatic matching algorithms were used. Initially the algorithms used for registration purposes were repeated and consistent solutions

were given. For the purpose of this study only one observer carried out the 'clipbox' definition. Manual matching requires significantly more time than the automatic matching algorithms and inter-observer variability is high [15]. The speed of the automated algorithms makes the move to on-line image correction more realistic in clinical practice.

Uncorrected rotational set-up errors in elongated targets could result in the PTV being compromised [36] and an increase in the received dose by critical structures (such as the spinal cord). The average PTV length for oesophageal cancers is 17 cm therefore rotations of 3 degrees could equate to a target displacement up to 5 mm. The maximum rotation observed in this group of patients was 9 degrees and rotations of greater than 3 degrees were observed on 33 (21.7%) of registrations (pitch, roll or yaw), using C-PTV. Rotations greater than 3 degrees can not be corrected even with a robotic treatment couch therefore patient repositioning or revision of the immobilisation should be considered in cases where significant rotations are frequent.

Additional investigations and revision of the 'clipbox' defined volume will be required when shape defined (masked) matching and the use of multiple 'clipboxes' are clinically available. The use of these tools potentially enables further refinement of match areas.

In conclusion the defined area for matching is important for oesophageal tumours. The alignment 'clipbox' and registration method selected can have an effect on the displacements (translations and rotations) obtained. These may best be determined from the tumour location within the oesophagus and highlights the need to diversify protocols within one tumour site. CBCT scans enable the assessment of tumour location, and consequently assisting in informing individualised registration volumes (i.e. volumes stratified by upper, mid and lower tumour position). Further analysis is required to verify carina as a tumour surrogate for mid oesophageal tumours. 3D volumetric imaging is now available in many radiotherapy departments and appropriate clinical protocols and personnel training needs to be a developed for mainstream use. Good knowledge of 3D anatomy is essential in order to verify accurate registrations and the provision of guidelines and high standards of training are fundamental to implementing CBCT IGRT. In conclusion, accurate verification of oesophageal tumours necessitates clinical protocols to be determined by tumour position.

Acknowledgements

We acknowledge NHS funding to the NIHR Biomedical Research Centre. Alexandra Aitken was part funded by Elekta Oncology Systems. Presented in part at: EPI2k8, Electronic Portal Imaging and Positioning Devices Conference, May 2008, San Francisco California and ESTRO27 annual meeting, European Society of Therapeutic Radiology and Oncology, September 2008, Gothenburg, Sweden.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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