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FULL PAPER

Asymmetric margin setting at the cranial and caudal sides in respiratory gated and non-gated stereotactic body radiotherapy for lung cancer

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Objective: To evaluate total errors, including setup errors, and tumour motion changes with a electronic portal imaging device (EPID) cine at the cranial and caudal sides in respiratory gated and non-gated radiotherapy.

Methods: Co-ordinates of the tumour centres (TCs) in the craniocaudal direction were obtained by using four-dimensional CT (4DCT) for each bin and EPID cine frame. During the 100% duty cycle (DC100), 50% duty cycle (DC50) and 30% duty cycle (DC30), both centred on the 50 phase, the co-ordinates of the TCs were compared at the most cranial and caudal positions on both 4DCT and EPID cine.

Results: During DC100, total errors were -0.2 ± 2.1 and 1.1 ± 2.6 mm at the cranial and caudal sides, respectively. During DC50, the corresponding values were -0.2 ± 2.1

and 1.7 ± 3.2 mm, respectively; during DC30, they were -0.1 ± 2.1 and 1.8 ± 2.9 mm, respectively. The tumour motion changes at the caudal side were strongly correlated with tumour motion observed on 4DCT during DC100 ($R^2 = 0.59$).

Conclusion: Total errors and tumour motion changes on the caudal side were larger than on the cranial side because of the patients' breathing levels. Owing to variations of the TCs at beam-trigger events, the larger margin was required at the caudal side in gated radiotherapy.

Advances in knowledge: Variations of the TCs were evaluated at the cranial and caudal sides separately. Providing some margins to compensate for tumour motion changes was a significant requirement at the caudal side in gated and non-gated radiotherapy.

INTRODUCTION

To avoid geometric errors in stereotactic body radiotherapy (SBRT), it is extremely important to accurately determine the internal target volume (ITV).¹ In general practice, four-dimensional CT (4DCT) has been used to detect patient-specific motion for determining ITV.² However, inter- and intrafractional tumour motion changes cannot be completely detected by using only 4DCT. Wolthaus et al³ insisted that it is not at all important to accurately determine the ITV because the ITV created by the 4DCT scan overestimated the influence of respiration during treatment. Taking the insistence into account, the planning target volume (PTV), compensating for daily setup errors and changes in tumour motion, should be defined to meet the various ITVs or clinical target volumes on planning CT.

Many institutions have employed an isotropic ITV-PTV margin of 5 mm in any direction for SBRT for lung cancer,^{4,5} although Olsen et al⁶ reported using an ITV-PTV margin of 5 mm

except for 1.0 cm in the craniocaudal (CC) direction; and Stauder et al⁷ used a 5- to 10-mm margin; and Janssen et al⁸ used a 5- to 8-mm margin in the CC direction. Many institutions have employed a symmetrical margin in any direction.

Some investigators suggested calculation recipes of margins to compensate for the tumour position error induced by setup error or tumour motion change in radiation therapy.^{9,10} Sonke et al¹¹ insisted that it was important to utilize a margin non-linear margin recipe for SBRT in patients with lung cancer. These recipes were used widely for margin calculations. Few studies have been carried out to separately calculate margins at the cranial and caudal sides. Oshiro et al¹² found that the target position is more stable at end expiration than at end inspiration. Margins to compensate for changes in tumour motion may, therefore, have to be asymmetric at the cranial and caudal sides.

Asymmetric margin setting should be considered for respiratory gated radiotherapy too. Phase shift at the caudal

side is one of the causes for errors in tumour positioning; therefore tumour positioning errors induced by phase shift should be measured when determining the margin setting for respiratory gated radiotherapy. Korreman *et al*¹³ evaluated intrafractional motion change of fiducial markers for respiratory gated radiotherapy based on external surrogate respiratory monitoring by means of fluoroscopy. They reported that variations in intrafractional motion during respiratory gated radiotherapy were larger than those during non-respiratory gated radiotherapy and that the margin to compensate for changes in tumour motion during respiratory gated radiotherapy was larger than that during non-respiratory gated radiotherapy. However, the setup error for the study was not measured because the analysis was not performed on a treatment bed.

No studies have been conducted to simultaneously evaluate both changes in tumour motion and daily setup errors during respiratory gated radiotherapy. For a calculation of the ITV-PTV margin to compensate for these two complications, an electronic portal imaging device (EPID) cine used after treatment setup proved to be useful.^{14,15} For the study reported here, we evaluated the position of the tumour centre (TC) at the cranial and caudal sides by using 4DCT during simulation and EPID cine images during treatment. The aim of our study was to separately evaluate the ITV-PTV margins required to compensate for inter- and intrafractional changes in tumour motion for respiratory gated radiotherapy and non-respiratory gated radiotherapy and the setup error at both the cranial and caudal sides.

METHODS AND MATERIALS

Subjects

Between October 2010 and November 2011, 60 patients underwent non-gated SBRT for Stage I non-small-cell lung cancer at Osaka Medical Center for Cancer and Cardiovascular Diseases. 15 of these patients (25%) who met the following 2 criteria were enrolled in this study: a lung tumour motion range of >5.0 mm on 4DCT at simulation and lung tumours well recognized on EPID cine during treatment. Patients were chosen retrospectively after treatment. Their median tumour size was 20 mm; their median age was 77 years; and the male-to-female ratio was 11:4. For this study, tumour positions were determined in the CC direction using the isocentre as the origin on 4DCT and EPID cine.

CT simulation and treatment

For simulation, every patient underwent 4DCT with a GE LightSpeed® instrument (16 slices: slice thickness 2.5 mm, a field of view 50 cm; GE Healthcare, Waukesha, WI). CT was equipped with a real-time position management (RPM) system (Varian® Medical Systems, Palo Alto, CA) that acquired displacements of an infrared-reflective marker (IRM) on the patient's abdomen. 4DCT generated eight slices of 2.5-mm thickness per gantry rotation in the axial cine mode. Breathing signals and CT images were loaded into the GE Advantage Sim Workstation (GE Healthcare), which generated 10 respiratory bins based on time-based sorting. Maximum intensity projection-CT and average intensity projection (AIP)-CT reconstructed from these 10 bins were then used for radiotherapy planning. The TC for each bin in the CC direction was defined as the midpoint of the upper and lower edges of the tumour. The delineation was performed by

a physician. The display settings for the determination of the edges of each tumour were congruent with the lung field (window level = -300 HU, window width = 1400 HU). In this study, the 50% phase was used as the middle phase of each duty cycle. During the 100% duty cycle (no gating: DC100), the 50% duty cycle centred on exhalation (gating window from 30% to 70%: DC50) and the 30% duty cycle centred on exhalation (gating window from 40% to 60%: DC30), the CC co-ordinates of the most cranial TC (CraTC-4DCT) and most caudal TC (CauTC-4DCT) were determined on the co-ordinate system where the planning beam centre was the co-ordinate origin. RM-4DCT was defined as the residual motion on 4DCT of each duty cycle (DC).

Radiation therapy planning was based on AIP-CT findings and executed with the Eclipse planning system v. 10 (Varian Medical Systems). To account for tumour motion, the tumour on maximum intensity projection-CT was defined as ITV. The isotropic margin of 5 mm was then added to the ITV to create PTV. Irradiation was delivered *via* seven non-coplanar photon beams of 6 MV with a beam aperture margin of 5 mm for a total prescribed dose of 48 Gy at the isocentre delivered in four fractions.

Treatment was delivered with a Varian 23EX linear accelerator equipped with a 60-leaf collimator, an aS1000 EPID and a gantry-mounted On-Board Imager® (Varian Medical Systems). Before each treatment, free-breathing cone beam CT (FB-CBCT) was used for localization. The FB-CBCT parameters were as follows: acquisition time of 1 min, matrix size of 512×512 pixel, slice thickness of 1 mm and a field of view of 45 cm in diameter in the axial plane and 16 cm in the CC direction. A physician manually registered the CBCT and ITV according to the tumour in three planes (transverse, coronal and sagittal).

To measure TC motion in the CC direction during treatment, EPID cine images were consecutively acquired through one beam whose parameters were a gantry angle of 0° or 180° or a couch angle of 0° . Beam dose rate was 10 MU s^{-1} (600 MU min^{-1}), and the averages of 82 EPID cine images of 4–9 respiratory cycles were acquired in 22 s at a rate of 1 frame per 0.267 s. The matrix size of the images was 768×1024 , and the pixel size 0.26×0.26 mm. The displacements of an IRM on a patient's abdomen were simultaneously recorded by the RPM system at a rate of 30 samples s^{-1} . We obtained these data sets in 4 sessions from 15 patients for a total of 60 sets. For this study, co-ordinates of the TC on EPID cine images (TC-cine) were obtained using an in-house software applying the template-matching technique.

Details of the in-house software

The EPID cine was transferred and analyzed offline using an in-house software after treatment. First, the search area was defined as a region that adequately showed the extent of lung tumour motion throughout the whole breathing cycle. Second, a template image was defined. The designation was carried out on a frame of the end-expiratory phase because this phase had minimal motion and good visibility of the tumour. Interobserver variation was analyzed by having two physicians designate a template consisting of a rectangular region of interest circumscribing the tumour shadow. The mean $\pm$ standard deviation (SD) of the difference in co-ordinates of the geometric centre of the

templates between two physicians was 0.6 ± 0.4 mm. Because the difference between the two physicians was small, automatic tracking was carried out using the template of only one of the two physicians.

Automatic tumour tracking was conducted for 60 EPID cine sets using the in-house software and the templates designated by one of the 2 physicians. For the remaining frames, an automatic search over the entire search area was conducted to identify a position for the template where the sum of differences in pixel intensity between the template and the frame image was minimal. The following formula was used:

$$D(x, y) = \sum_{i=0}^{M-1} \sum_{j=0}^{N-1} \{I(x+i, y+j) - T(i, j)\}^2$$

where $D(x, y)$ is a sum of differences in pixel intensity between the template and the frame image when the co-ordinates of the left-upper corner of the template are (x, y) . M and N are the length and width, respectively, of the template image. $I(i, j)$ is the pixel intensity at location (i, j) of the search area and $T(i, j)$ is the template image at location (i, j) . In this system, the co-ordinate origin was the centre of the EPID flat panel that corresponded to the central axis of the radiation fields.

Phantom study

To synchronize tumour motion on EPID cine and displacements of an IRM, the acquisition time of each system had to be determined. To this purpose, the RPM system recorded a trigger signal as the time of irradiation, and with a constant sampling rate of a 30 samples s^{-1} , the acquisition time of each point of an IRM could be identified by the sampling number. On the other hand, the acquisition time of each EPID cine frame could not be identified by the frame number because the beam dose rate during the rise time was not constant. We, therefore, performed a phantom study to determine the relationship between the acquisition time and EPID cine frames.

For the phantom, the Quasar Respiratory Motion Platform (Modus Medical Devices Inc., ON, Canada) was used, which was composed of two synchronously moving plates. One plate that moved horizontally is mounted with a cork box on it, which contains a water equivalent ball of 3 cm in diameter, whereas the other plate with an IRM on it fluctuates vertically. The motion parameters were a 4-s cycle and amplitude of 10 mm, and the motion pattern of the plates was a biquadratic sinusoidal waveform. This phantom system was set on the treatment couch with the moving centre of the target ball at the isocentre. The radiation portal was 6 cm wide and 8 cm long with a gantry angle of 0° , and the radiation time was about 11 s. EPID cine and displacements of an IRM were acquired 20 times under the same conditions as for patient treatment. The centre of the target ball on each EPID cine frame was determined using in-house software.

The rise time of the treatment machine used in our study was preliminarily measured. We assumed that most of the rise time was used to acquire the first frame, and the subsequent frames were acquired at a constant rate of one frame every 0.267 s.

Based on these assumptions, the interval between the trigger time and the centre of the n th frame acquisition time (t_n) was represented using the formula:

$$t_n = T_1 + (n - 2)T_n + 0.5T_n (n \geq 2) \quad (1)$$

where T_1 and T_n are the imaging time of the first frame and each subsequent frames (0.267 s), respectively. Figure 1a shows displacements of an IRM (solid line) and of the ball target centre on EPID cine (dotted lines) in relation to T_1 . Each dotted line shows displacement of the ball target for T_1 of 0.3, 0.4 and 0.6 s. When the solid lines and the dotted lines matched, the cross-correlation value between displacements of the IRM and the ball target on EPID cine was the highest, and T_1 was the actual acquisition time of the first frame. Figure 1b shows changes in cross-correlation (Crc) values between the displacement of an IRM and the ball target for T_1 . The mean of T_1 values with the highest Crc in 20 data sets was used in the clinical study.

Data analysis

The phantom study was used to define T_1 , which in turn was used to synchronize the tumour motion with an IRM signal for

Figure 1. A method for T_1 estimation. (a) Displacements of a tumour and an infrared-reflective marker (IRM) on a common temporal axis. The solid line shows IRM displacement. Dotted lines show displacements of the tumour in electronic portal imaging device (EPID) cine. The T_1 is the imaging time of the first frame. The Crc is cross-correlation value between the displacement of an IRM and the ball target. (b) The relationship between T_1 and the correlation of tumour displacement with that of an IRM is shown. For T_1 of 0.427 s, the Crc was the maximum of 0.998. ■: $T_1 = 0.1$ s, ▲: 0.4 s and ●: 0.6 s.

a clinical case. In the CC co-ordinate, the most cranial TC (CraTC-cine) and most caudal TC (CauTC-cine) values on EPID cine were determined during each DC as defined by an IRM phase on the co-ordinate system, which is fixed so that the image centre was the origin. Differences in TC at the cranial and caudal sides were calculated using the formulas:

$$\Delta\text{CraTC} = \text{CraTC-cine} - \text{CraTC-4DCT}$$

and

$$\Delta\text{CauTC} = \text{CauTC-cine} - \text{CauTC-4DCT}$$

in which ΔCraTC and ΔCauTC are assumed to represent total errors including both changes in TC motion and the setup error. For any DC, the two ends of the TC position were named CraTC-cine and CauTC-cine, respectively, and the TC motion range was named RM-cine. The accuracy of automatic tracking using the in-house software was assessed at the second session by comparing RM-cine and mean tumour position on EPID cine images (MTP-cine) between automatic and manual tracking. The differences in RM-cine and MTP-cine between automatic and manual tracking were 0.3 and 0.1 mm on average, respectively.

The means of TC positions on the 10 bins of 4DCT and for each frame on the full-phase EPID cine were termed mean tumour position-4D (MTP-4DCT) and MTP-cine, respectively. The difference between MTP-cine and MTP-4DCT was assumed to reflect the setup error ($\Delta\text{MTP} = \text{MTP-cine} - \text{MTP-4DCT}$) for each DC.

To detect variations in tumour motion changes, ΔCraTC and ΔCauTC were normalized by ΔMTP . $\Delta\text{CraTC\#}$ and $\Delta\text{CauTC\#}$ were calculated, respectively, using the formulas. $\Delta\text{CraTC\#}$ and $\Delta\text{CauTC\#}$ represented changes in TC motion.

$$\Delta\text{CraTC\#} = \Delta\text{CraTC} - \Delta\text{MTP}$$

and

$$\Delta\text{CauTC\#} = \Delta\text{CauTC} - \Delta\text{MTP}$$

A positive value derived with either of these formulas mean TC-cine is more caudal than TC-4D. Total errors, tumour motion change and setup errors were expressed in terms of systematic (Σ) and random (σ) errors for ΔCraTC , ΔCauTC , $\Delta\text{CraTC\#}$, $\Delta\text{CauTC\#}$ and ΔMTP . The margins to compensate for ΔCraTC , $\Delta\text{CraTC\#}$, ΔCauTC , $\Delta\text{CauTC\#}$ and ΔMTP were calculated using Stroom's formula:⁹

$$\text{Margin} = 2\Sigma + 0.7\sigma \quad (2)$$

The margins calculated by Stroom's formula were for the 95% isodose to enclose 99% of the clinical target volume. Another margin recipe,¹⁰ also, published given by:

$$\text{Margin} = 2.5\Sigma + \beta\sqrt{\sigma^2 + \sigma_p^2} - \beta\sigma_p \quad (3)$$

where σ_p is the width of the penumbra modelled by a cumulative gaussian, and σ_p was 6.4 mm in the lung. β is the value of

the inverse cumulative standard normal distribution at the prescribed PTV minimum dose level and $\beta = 0.84$ should be used in SBRT for the lung. The margin required to compensate for random errors was affected by tissue.^{11,16} To derive margin recipe for SBRT of patients with lung cancer, it is important to use non-linear recipe.

Other uncertainties, such as mechanical accuracy of the linear accelerator or interobserver setup-matching errors, were evaluated for the calculation for overall margins. The overall Σ , the root sum of squares Σ s of total errors and of other uncertainties, and the overall σ , the root sum of squares σ s of total errors and of other uncertainties, were calculated for overall margins at the cranial and caudal sides separately.

RESULTS

Phantom study

The rise time in our treatment machine proved to be approximately 0.4 s. For 20 time measurements, the average T_1 with the highest cross-correlation value was 0.42 s (range: 0.39–0.46 s; SD: 0.03 s), whereas the cross-correlation value was nearly 1.0. Consequently, a T_1 of 0.42 s was used for the patient study.

Clinical study

Each frame in EPID cine was given an acquisition time parameter by determining the T_1 , so that both displacements of the tumour on EPID cine and of an IRM on the patient's abdomen could be synchronized on the same temporal axis. Figure 2 shows three curves: the solid line is the IRM amplitude signal; the saw-tooth line is the IRM phase signal; and the dotted curve is the tumour respiratory motion. Grey areas represent irradiation time, and the edges of these areas represent beam trigger timing defined by the IRM phase signal.

The mean values and SDs of RM-4D were 10.9 ± 7.7 , 4.4 ± 4.6 and 2.3 ± 2.5 during DC100, DC50 and DC30, respectively, and the corresponding values of RM-cine were 9.8 ± 5.9 , 2.5 ± 2.1 and 0.5 ± 0.8 , respectively. For every DC, the mean of RM-cine was thus significantly larger than RM-4D (paired t -test: $p < 0.05$). The mean values and SDs of ΔRM were 0.9 ± 2.5 , 2.1 ± 2.9 and 2.1 ± 2.2 , and they were larger during DC50 and DC30 than during DC100. The mean values and SDs of ΔMTP were 0.2 ± 2.4 mm.

In most cases, TC-cine on the caudal side was unstable but was stable on the cranial side (Figure 2). Table 1 shows mean values and SDs (range: min–max) of $\Delta\text{CraTC\#}$, $\Delta\text{CauTC\#}$, ΔCraTC and ΔCauTC . The means of ΔCauTC and $\Delta\text{CauTC\#}$ were significantly larger than those of ΔCraTC and $\Delta\text{CraTC\#}$ ($p < 0.01$). In addition, the means of ΔCauTC and $\Delta\text{CauTC\#}$ were larger for DC30 and DC50 than for DC100. During DC50, in particular, trigger events occurred when the tumour motion was steep (Figure 2). Hence, subtle changes in respiratory motion pattern led to major deviations in TC position. Figure 3 shows histograms of total errors at the two sides. At the cranial side, there were almost the same values for ΔCraTC for each DC. At the caudal side, the total errors for respiratory gated radiotherapy were larger than those for non-respiratory gated radiotherapy, whereas for the latter, the ratio of the cases with errors of >6.0 mm was 26.7% for DC50 and 20.0% for DC30.

Figure 2. The methods for measuring the most cranial and most caudal tumour centres (TCs) on electronic portal imaging device (EPID) cine were determined during respiratory-gated radiotherapy with the 50% duty cycle centred on exhalation (gating window from 30% to 70%: DC50) as defined by an infrared-reflective marker (IRM) phase. The solid curve represents the respiratory wave of an IRM and the dotted curve represents the tumour on EPID cine. Grey areas represent the gating window defined by the phase signal of the sawtooth dotted line. The TC in the grey area at the most cranial side, shown as a dotted circle, is CraTC-cine and at the most caudal side TC, shown as a solid circle, is CauTC-cine. The residual motion (RM-cine) shows the peak-to-peak motion of TC-cine.

Figure 4 shows the relationships between RM-4D and tumour motion changes at each side for every DC. R^2 was 0.02, 0.09 and 0.01 for DC100, DC50 and DC30, respectively, at the cranial side, showing no correlation between RM-4D and Δ CraTC during any DC. R^2 at the caudal side was 0.59, 0.19 and 0.05 for DC100, DC50 and DC30, respectively, with a strong correlation for DC100 and no correlation for DC50 and DC30. There was no correlation between RM-4D and Δ MTP ($R^2 = 0.02$). The setup error and tumour motion changes at the cranial side did not correlate with RM-4D for any DC.

Setup margin in the CC direction was calculated on the basis of Δ MTP. Margins based on Δ CauTC# and Δ CraTC# to compensate for tumour motion changes were calculated separately for the cranial and caudal sides. Total margins to compensate for the total errors comprising both tumour motion changes and setup error were obtained by means of Δ CauTC and Δ CraTC. Table 2 shows Σ , σ and margins for the setup error, tumour motion changes and total errors. At the cranial side, systematic and random errors of tumour motion changes and total errors were the same for every DC. At the caudal side, these errors

varied with the DC and were larger than those on the cranial side. Margins to compensate for tumour motion changes and total errors at the caudal side were >2 mm larger than those at the cranial side. The total margin at the caudal side during DC50 was the largest of all margins established in this study.

Weekly quality assessment showed that the mechanical error between the centre of the EPID flat panel and the central axis of fields was -0.1 ± 0.2 mm. The mean for the interobserver setup matching errors was -0.1 ± 0.5 mm. Σ , σ and margins for overall uncertainties appear in Table 2. These margins were almost the same as the margins to compensate for total errors for each DC in both sides.

DISCUSSION

For SBRT, some institutions set margins that are symmetric in all directions. For example, the ITV-PTV margin was set at 5 mm in all directions for the RTOG 0915, whereas Guckenberger et al⁴ and Taremi et al⁵ used 4DCT for defining ITV and CBCT for localization and changed the ITV-PTV margin by adding 5 mm in all directions. However, conversion of the ITV-PTV margin for targets with respiratory motion, such as lung tumours, must include the setup margin and also a margin that is set to account for variations in tumour motion, which have a particularly strong effect on the margin in the CC direction. Therefore, some institutions set the margin larger in the CC direction than in the other directions. Olsen et al⁶ set the margin at 5 mm in the anteroposterior and right-left directions but at 10 mm in the CC direction. Similarly, Stauder et al⁷ set the ITV margin at 5 mm in the anteroposterior and right-left directions but at 5–10 mm in the CC direction. Furthermore, Janssen et al⁸ set a margin at 5–8 mm in the CC direction, which was slightly larger than those in other directions. However, no studies have investigated these margins in detail, although they evaluated the setup error and the variations in tumour motion separately. Moreover, since the stability of respiratory motion differs at the cranial and caudal sides, the required margins are not always symmetric. We compared the centre of a tumour during treatment planning with that during treatment and examined the margin that compensated for the variation in tumour motion at the cranial and caudal sides, first without and then with inclusion of the setup error.

Table 1. Mean $\pm$ standard deviation (min, max) for tumour motion variations and total error

	Cranial side	Caudal side
Tumour motion variations	Δ CraTC#	Δ CauTC#
DC100	0.0 ± 0.9 (−1.6, 1.2)	1.2 ± 1.8 (−1.5, 4.8)
DC50	0.0 ± 0.9 (−1.5, 1.2)	1.9 ± 2.8 (−0.6, 8.4)
DC30	0.1 ± 0.9 (−1.5, 1.2)	2.0 ± 2.1 (−0.2, 7.6)
Total error	Δ CraTC	Δ CauTC
DC100	-0.2 ± 2.1 (−5.5, 2.6)	1.1 ± 2.6 (−3.4, 4.6)
DC50	-0.2 ± 2.1 (−5.5, 2.6)	1.7 ± 3.2 (−3.7, 8.7)
DC30	-0.1 ± 2.1 (−5.4, 2.6)	1.8 ± 2.9 (−3.6, 7.9)

Δ CraTC# and Δ CauTC# are changes in TC motion at cranial and caudal side.

Figure 3. Histograms of total errors of the tumour centre (TC) position at the caudal side (a) and at the cranial side (b) during each duty cycles (DCs).

We also evaluated tumour motion changes from TC-cine and TC-4D normalized for each MTP. Non-respiratory gated radiotherapy cases showed a significantly larger mean difference (0.8 mm) in TC-cine at the caudal side than at the cranial side while 1SD was also larger at the caudal side. These results were similar to those reported by Oshiro et al.¹² In other words, the end-expiratory position of a tumour was stable, whereas the end-inspiratory position of the tumour showed major variations.

The baseline position shift at the cranial side during treatment should also be taken into consideration. ITV created for 4DCT does not completely accurately represent tumour motion such as baseline shift during treatment. In our study, only one beam was used for analysis, so it is possible that baseline shift was not detected. Ge et al.¹⁷ reported that the intrafractional change in baseline position was up to 2.2 mm with a median value of 1.0 mm in the CC direction. Our measurements indicated that at the cranial side, the ITV-PTV margin of 5.0 mm was needed.

A margin of 1 or 2 mm might be added to compensate for the baseline position shift. However, devices and technological developments such as the flattening filter-free beam and volume-modulated radiotherapy can shorten irradiation time, so that the tumour position errors resulting from the baseline position shift will be small when such techniques and devices are used.^{18,19}

It has been introduced that the difference in tumour motion between planning and treatment did not depend on tumour

Figure 4. Relationships between ΔCauTC , ΔCraTC and residual motion on four-dimensional CT (RM-4D) at planning each duty cycle (DC), (a): DC100, (b): DC50 and (c): DC30. ΔCraTC and ΔCauTC are assumed to represent total errors including both changes in tumour centre motion and the setup error. ΔCauTC during DC100 was strongly correlated with RM-4D ($R^2 = 0.5881$), and ΔCraTC showed no correlation with RM-4D for any duty cycles. ΔCraTC and ΔCauTC are total errors at cranial and caudal side.

Table 2. Σ , σ for setup errors, tumour motion changes, total errors and overall uncertainties

Errors	Directions	DC	Σ	σ	Margins	
					Equation 2	Equation 3
Setup errors		DC100	1.8	2.0	5.2	5.7
		DC50	1.9	1.9	5.1	6.0
		DC30	2.2	1.8	5.7	6.6
Tumour motion changes	Cranial	DC100	0.9	0.8	2.4	2.6
		DC50	0.7	0.6	1.9	2.1
		DC30	0.6	0.5	1.5	1.6
	Caudal	DC100	1.8	1.9	5.0	5.7
		DC50	2.6	2.1	6.5	7.1
		DC30	1.5	1.2	3.8	4.3
Total errors	Cranial	DC100	2.1	1.7	5.4	6.3
		DC50	2.1	1.7	5.4	6.2
		DC30	2.1	1.7	5.3	6.2
	Caudal	DC100	2.6	3.2	7.4	8.7
		DC50	3.2	3.2	8.7	10.3
		DC30	2.9	2.4	7.5	8.8
Overall uncertainties	Cranial	DC100	2.1	1.8	5.5	6.4
		DC50	2.1	1.7	5.5	6.4
		DC30	2.1	1.8	5.4	6.3
	Caudal	DC100	2.6	3.3	7.5	8.8
		DC50	3.2	3.3	8.7	10.3
		DC30	2.9	2.4	7.6	8.9

DC, duty cycle.

Margins to compensate for these errors were calculated using Equations (2) and (3) for three DCs.

Equation (2): margin = $2\Sigma + 0.7\sigma$; equation (3): margin = $2.5\Sigma + \beta\sqrt{\sigma^2 + 0.64^2} - 0.54$.

motion during treatment planning, although tumour motion was not examined separately at the cranial and caudal sides in a previous report.¹⁴ In addition, the peak-to-peak tumour motions, in most cases, were <5 mm, which is the smallest value observed in our study. Korreman et al²⁰ examined the relationship between tumour motion and margin and determined that the size of the margin needed to be increased as the tumour motion increased; especially when the tumour motion exceeded 10 mm, a positive correlation was observed between tumour motion and margin. However, this study again did not examine the tumour position errors at the cranial and caudal sides separately, nor did it do so for setup error and errors due to variations in tumour motion. We found that tumour position errors at the caudal side increased as tumour motion increased during DC100, which was similar to the finding reported by Korreman et al.²⁰ However, our study revealed that the setup error and tumour motion changes at the cranial side did not depend on tumour motion in the simulation.

The margin necessary to compensate for variations in tumour motion was approximately 2 mm at the cranial side and >4 mm

at the caudal side. The total margin, which included the margin added to compensate for variations in tumour motion, was 6.0 mm at the cranial side and 8.0 mm at the caudal side. Since the ITV-PTV margin of 5 mm can only compensate for the setup error, this value was therefore considered to be too small at the caudal side, where the effect of the variations in tumour motion was especially strong. The results obtained in our study lead us to recommend that margins at the cranial and caudal sides should be asymmetric; *i.e.* larger at the caudal side than at the cranial side. A margin of 5 mm at the caudal side, as set by Guckenberger et al⁴ and Taremi et al,⁵ is thus probably too small and the margin of 10 mm at the cranial side set by Olsen et al⁶ is probably too large.

The setup margin is affected by the setup method. Many reports have examined the usefulness of CBCT and 4DCT in SBRT for localization of soft tissue or tumour. For example, Suzuki et al²¹ reported that tumour shifts resulting from localization with bony anatomy became larger in accordance with the distance between the vertebra and the tumour, so that the localization with bony anatomy is considered not useful. A method using 4D

CBCT images, as reported by Takahashi et al²² and Sweeney et al²³, may be able to reduce margin size more effectively than can be achieved with FB-CBCT methods. Korreman et al²⁰ reported that a method using 4DCT and 4D CBCT images could minimize the required margin size more effectively compared with existing techniques. In our study, FB-CBCT and AIP images were used for localization in SBRT, and the accuracy of this method can be rated comparatively high among existing setup methods.

The margin at the cranial side to compensate for tumour motion changes and total errors was the same for respiratory gated radiotherapy as for non-respiratory gated radiotherapy. However, the variations at the caudal side were larger for respiratory gated radiotherapy than for non-respiratory gated radiotherapy. Nelson et al²⁴ obtained several 4DCT images on different days and used them for tumour positioning for the ITV-PTV margin and found that the ITV-PTV margin was smaller for respiratory gated radiotherapy than for non-respiratory gated radiotherapy. There seem to be two reasons for this discrepancy with our finding.

The first is that in the case of 4DCT, CT of each phase is retrospectively sorted after the waveform of the motion pattern of the abdominal wall has been obtained. For respiratory gated radiotherapy, on the other hand, the actual direct current for irradiation is prospectively determined on the basis of the waveform of the abdominal motion pattern immediately before irradiation. Consequently, the actual waveform may differ from the predicted waveform. Moreover, the position of the tumour can vary greatly in spite of the small difference between the waveforms because beam trigger events occur when the slope of the waveform is steep. For respiratory gated radiotherapy, a margin must, therefore, be added at the caudal side to compensate for the variations in the TC location resulting from the effect of tumour position variations at trigger events. The Nelson study did not take this additional error induced by tumour position variations at trigger events into consideration. The second reason for the discrepancy is that the use of 4DCT allows measurement of the respiratory waveform of only one cycle. In other words, only the interfractional error could be measured.¹⁷ We observed the respiratory waveforms of several cycles and calculated margins where the intrafractional error was added to the interfractional error so that the margin at the caudal side was larger for respiratory gated radiotherapy than for non-respiratory gated radiotherapy.

Redmond et al²⁵ found by three rounds of 4DCT scans that phase offset between gross tumours were significantly different. The interfractional difference in phase offset is held responsible for increasing margin magnitude compensated for tumour position errors in respiratory gated radiotherapy. According to the study carried out by Bedder et al,²⁶ respiratory gating at the end of expiration (*i.e.* the 40–60% phases) may therefore be the most precise. In our study, at DC30, margins compensated for total errors or tumour motion change at the end of expiration gating were smaller than those at DC50.

Redmond et al²⁵ reported that excursions of gross tumour volume between simulation and rescan were stable on 4DCT. Guckenberger et al²⁷ demonstrated that tumour motion change was the largest in the CC direction but was no more than 2 mm

on interfractional tumour motion change using repeated planning 4DCT. In these studies, tumour motions were acquired using repeated 4DCT. However, it was reported by Ge et al¹⁷ that tumour motion during 4DCT scan cannot adequately represent tumour motion during treatment, especially in the case of patients with SBRT. They acquired tumour motions during treatment using fluoroscopy. In most cases in our study, the tumour motion on 4DCT was underestimated during treatment. We believe that the margin was required to compensate for the uncertainty of the ITV created by 4DCT as the ITV-PTV margin. In our study, the margin was required more at the caudal side than at the cranial side.

Schaake et al²⁸ evaluated interfractional tumour motion change using 4D CBCT. They found that the peak-to-peak tumour motion was larger during treatment than during simulation and proved that the size of the margin compensated for tumour motion change needed to be increased as the tumour motion increased. In our study, the magnitude of interfractional tumour motion change was larger at the caudal side than at the cranial side. It was found that the margin only at the caudal side depended on the magnitude of tumour motion.

Oshiro et al¹² used radiation perspective images to measure the position of a metal marker in the liver during treatment in order to determine the variation in target position during expiration. They then calculated the margin by comparing the position of the target during actual treatment with that during treatment planning¹¹ and found that a margin of 4.6 mm was required at the caudal side in the CC direction. They compared the average motion of the metal marker during respiratory-phase synchronous irradiation among prospective images and calculated the required symmetric margins at the cranial and caudal sides. Our value for the margin at the cranial side was similar to theirs, but for the margin at the caudal side, our value was larger than theirs. The reason for this discrepancy may be that, since Oshiro et al¹² compared average values obtained during irradiation, the degrees of deviation at the caudal side was also averaged, so that their value was smaller than ours.

CONCLUSION

We used EPID cine for separate assessments of TC variations at the cranial and caudal sides for respiratory gated radiotherapy and non-respiratory gated radiotherapy. Patient breathing level during the inspiratory phase proved to be less stable than during the expiratory phase. Moreover, the TC position error during respiratory gated radiotherapy was induced by a timing error of the beam trigger events at the caudal side. These conditions could be the reason for the greater variations at the caudal side during both respiratory gated radiotherapy and non-respiratory gated radiotherapy. As a result, margins to compensate for the errors should be larger for the caudal side than for the cranial side.

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