Uncertainty in patient set-up margin analysis in radiation therapy

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We investigated the uncertainty in patient set-up margin analysis with a small dataset consisting of a limited number of clinical cases over a short time period, and propose a method for determining the optimum set-up margin. Patient set-up errors from 555 registration images of 15 patients with prostate cancer were tested for normality using a quantile-quantile (Q-Q) plot and a Kolmogorov–Smirnov test with the hypothesis that the data were not normally distributed. The ranges of set-up errors include the set-up errors within the 95% interval of the entire patient data histogram, and their equivalent normal distributions were compared. The patient set-up error was not normally distributed. When the patient set-up error distribution was assumed to have a normal distribution, an underestimate of the actual set-up error occurred in some patients but an overestimate occurred in others. When using a limited dataset for patient set-up errors, which consists of only a small number of the cases over a short period of time in a clinical practice, the 2.5% and 97.5% intervals of the actual patient data histogram from the percentile method should be used for estimating the set-up margin. Since set-up error data is usually not normally distributed, these intervals should provide a more accurate estimate of set-up margin. In this way, the uncertainty in patient set-up margin analysis in radiation therapy can be reduced.

Keywords: Prostate; set-up error; SM; PTV

INTRODUCTION

In intensity-modulated radiation therapy (IMRT), it is possible to achieve a high dose distribution that closely conforms to the target shape, thus increasing the possibility of a complication-free cure. In order to ensure that the target receives the precise dose in the presence of geometrical errors, such as those owing to patient set-up and organ motion, a margin is applied to the clinical target volume (CTV) when generating the planning target volume (PTV) [1, 2].

To account for the physical motion of the target and patient set-up error, the internal margin (IM) and set-up margin (SM) are necessary when defining the PTV. Quantifying these margins during planning is necessary for calculating adequate PTV margins. These margins become more critical when IMRT, hypofractionation or dose escalation is considered [3]. A reduction of margins is possible by adequate use of image-guided techniques that allow online or offline correction protocols. An online correction protocol enables daily correction of both systematic and random (day-to-day) errors but increases the treatment time. Offline protocols that correct systematic errors provide a more efficient strategy for routine treatments in a busy department by minimizing image acquisition and analysis [4–6]. Generally, systematic error can be corrected for the individual patient using offline correction. However, for the PTV margin, deviations in the systematic error obtained between patients play an important role.

In order to determine the PTV margin, patient set-up errors are typically evaluated and analyzed assuming a normal distribution [2, 7]. However, when a different region is treated with radiation or another technique is applied (e.g. IMRT and other image-guided treatments), the PTV is

only determined during the early stages of its implementation. In this case, patient set-up errors are determined using a small number of clinical cases over a short period of time. Therefore, patient set-up errors may not always be normally distributed. Using the assumption of a normal distribution may result in inaccurate estimates of the PTV margin.

In this study, patient set-up error data were first evaluated for normality. For offline corrections, we demonstrate the uncertainty of patient set-up margin analysis in radiation therapy when assuming a normal distribution. Moreover, an analysis method for determining the optimum set-up margin is proposed.

MATERIALS AND METHODS

An X-ray image-guided system, the Novalis Body system (BrainLAB AG, Feldkirchen, Germany), was used in setting up patients included in this study. This system is made up of an infrared and an X-ray imaging component. The infrared component consists of two infrared cameras mounted on the ceiling of the treatment room for monitoring patient position based on the real-time location of infrared reflective markers placed on the patient's skin or on thermoplastic shells. The X-ray imaging component consists of two floor-mounted kV X-ray tubes that generate an X-ray field projected obliquely from lateral to medial, posterior to anterior, and superior to inferior onto two corresponding flat panel detectors suspended from the ceiling (Fig. 1).

After the initial patient set-up, two stereoscopic X-ray images are obtained using the 2-kV X-ray tubes in the
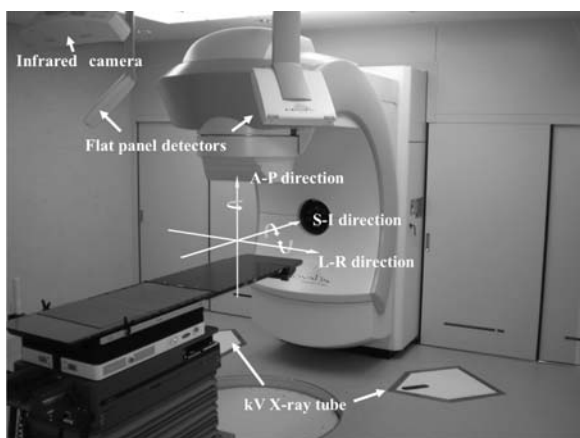
Fig. 1. The Novalis body system. The Novalis body system consists of two components for image-guided radiotherapy: an optical infrared (IR) tracking system and an X-ray unit. The latter consists of two floor-mounted kV X-ray tubes that can project radiation along the medial, anterior–oblique and inferior–oblique directions onto two corresponding ceiling-mounted amorphous silicon flat panel detectors. Shown here are the reference directions for patient and couch movement.

Novalis body system. These images are then compared with the digitally reconstructed radiographs (DRR) reconstructed from three-dimensional (3D) computerized tomography (CT) images taken during the simulation in order to determine the isocenter. The six degrees (6D) fusion software implemented in the Novalis body system first generates various sets of DRRs with position variations in both three translational and three rotational directions (six degrees of freedom) for CT images. The software compares these DRRs with the corresponding X-ray images and obtains the set of DRRs with the maximal similarity to the corresponding X-ray images. The three translational and three rotational position variations used to generate the set of DRRs are the 6D offsets used for fusing the images. In a phantom study, Jin *et al.* demonstrated that the maximal random error of this system was ±0.6 mm in each direction with a 95% confidence interval, while the systematic error was approximately 0.4 mm, mainly in the superior–inferior direction [8].

We analyzed patient set-up errors from 555 registration images of 15 patients (74 Gy/37 fraction) with prostate cancer. Each patient was immobilized with the HipFix®, Vac-Lok™ and Thermoplastics (CIVCO Medical Solutions, IA, United States) devices (Fig. 2a).

Patient set-up and image verification were performed as follows:

(1) The patient was immobilized using the same Vac-Lok, Hip-fix and Thermoplastics used when the planning CT images were taken (Fig. 2b and c).

(2) The positions of the infrared markers placed on top of the thermoplastics were used as bases for patient set-up localization (Fig. 2d).

(3) X-ray images from two directions were taken. These images were automatically registered to the corresponding DRRs with the aid of the 6D fusion software. From the image registration, the set-up error along the lateral (L–R), superior–inferior (S–I), and anterior–posterior (A–P) directions were determined. If an error exceeding 2 mm was observed, the couch was adjusted accordingly. The rotational errors were found to be negligible and so were recorded, but not used.

The set-up error acquired from the 6D fusion software was analyzed in the following steps. First, systematic errors were computed for individual patients from 37 treatments retrospectively. Second, the systematic errors were subtracted from all first set-up errors for individual patients. Subtracted set-up errors were assumed to be corrected set-up errors. Third, all patient corrected set-up errors were evaluated.
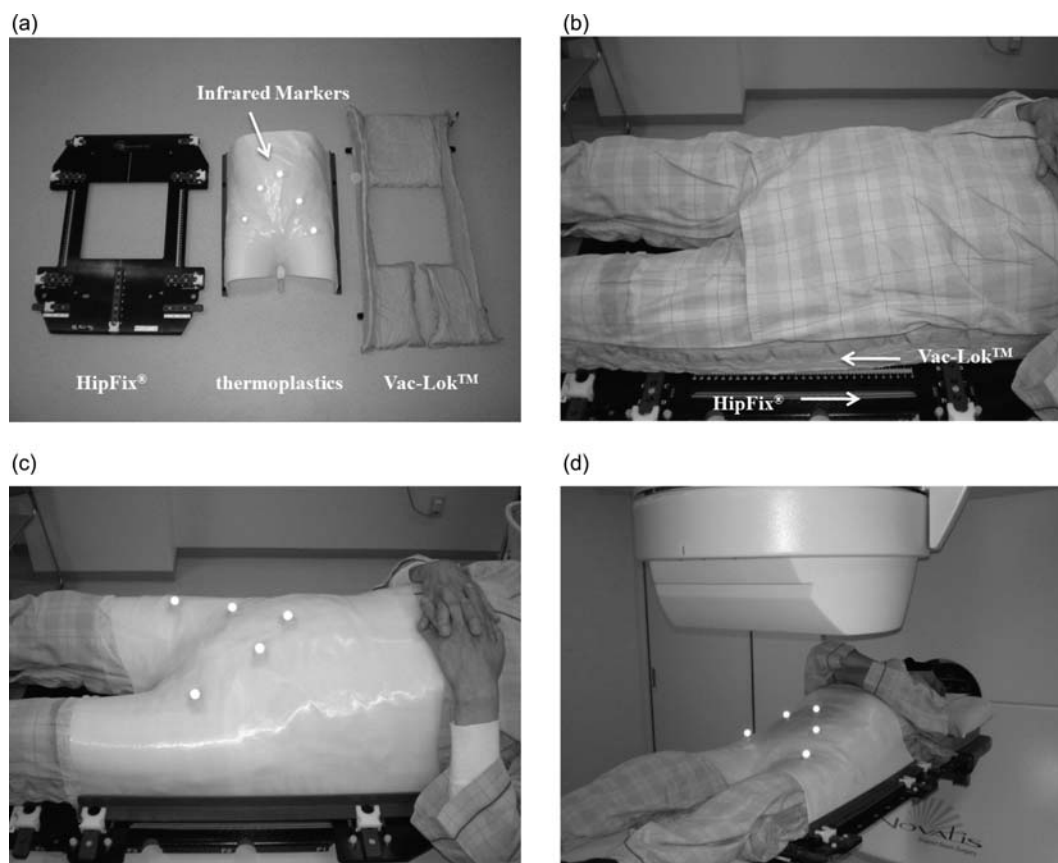
Fig. 2. Immobilization device for prostate IMRT irradiation consisting of the HipFix® baseplate, thermoplastic and Vac-Lok™ cushions. Infrared markers are placed on the thermoplastic shell as indicated by the arrow (**a**). The patient is made to lie on the Vac-Lok™ supported by the HipFix® baseplate as shown in (**b**). Infrared markers are placed on the thermoplastic shell, as shown in (**c**), after the latter is attached to the HipFix®. Shown in (**d**) is the patient position after the couch is automatically moved using the Novalis body system.

Normality test of patient set-up errors

Corrected systematic patient set-up errors were tested for normality using a Q-Q plot as a qualitative evaluation method. For quantitative evaluation, we performed the Kolmogorov–Smirnov test with the hypothesis that the data were not normally distributed.

The ranges of set-up errors from normal distributions and histograms

After the test for normality, histograms of the raw set-up errors for the patient population were plotted and the ranges of set-up errors (RSE) that included 95% of all the data (95% RSE) were determined for each direction. The ranges computed from the histogram were compared with the corresponding ranges assuming a normal distribution at a 95% confidence level, including 95% of all patient set-up error data in each direction

The ranges of set-up errors from histograms

The percentile method was applied in computing the RSE that included 95% of the histogram for all actual patient set-up error data. This was carried out by taking the range corresponding to the 2.5% and 97.5% interval of the histogram.

Confidence interval from normal distributions

The 95% confidence interval when the patient set-up error is assumed to be a normal distribution, 95% CI_{norm}, was calculated using equation 1.

$$\text{Range of 95\% confidence interval} = 2 \times 1.96\Sigma \qquad (1)$$

Where Σ is the standard deviation of a population (i.e. the preparation or systematic error). A 95% confidence interval corresponds to 1.96Σ.

RESULTS

Normality test of patient set-up errors

Except in a very narrow interval, the error distributions were not standard normal distributions. In the L–R and S–I directions, points in the Q-Q plot lie roughly on a line only within ±2 and ±15 mm, respectively. Beyond these distances, the tails of the distributions strongly deviate from a
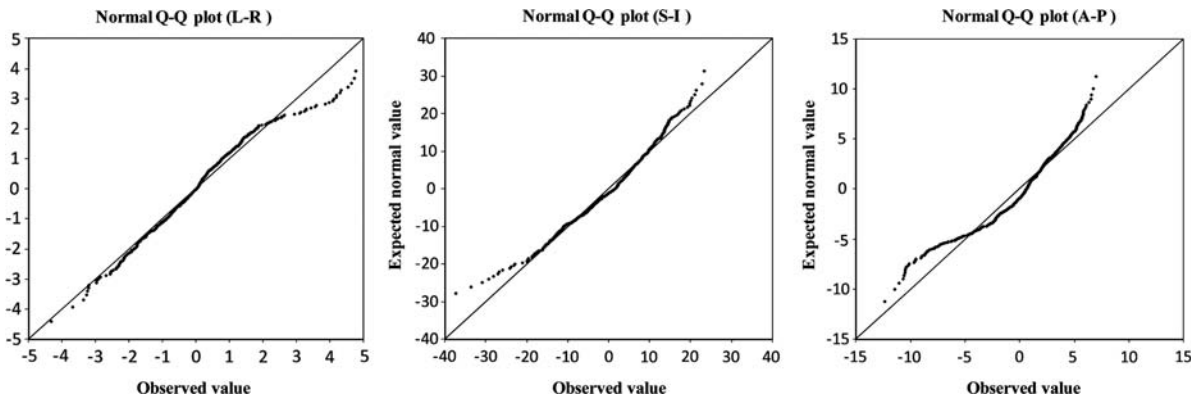
Fig. 3. Normal Q-Q plot of the patient set-up error for each direction. The Q-Q plot compares the observed distribution of set-up errors to a normal distribution.
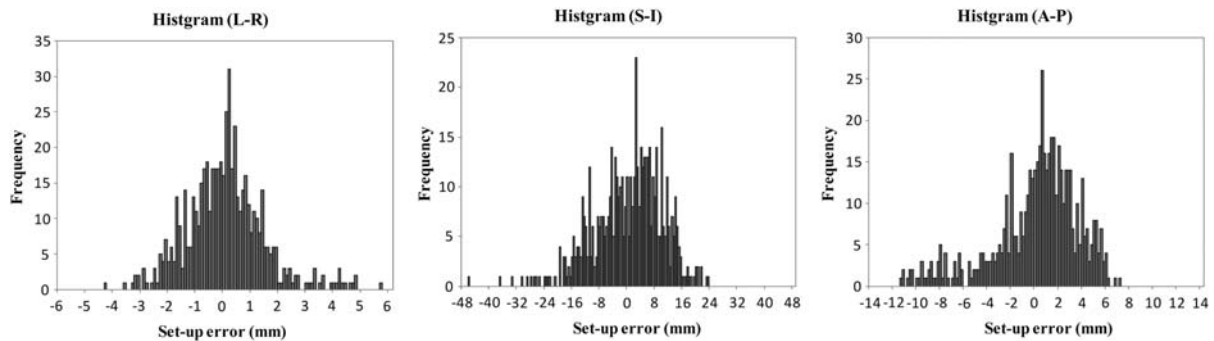
Fig. 4. histograms of the patient set-up error in each direction. Positive set-up error values indicate the left, superior and anterior directions for the L–R, S–I and A–P histograms, respectively. Negative set-up error values indicate the right, inferior and posterior directions, respectively.

straight line (Fig. 3), indicating that the error distributions are not standard normal distributions. Similarly, in the Kolmogorov–Smirnov test, we found that each of these error distributions was not normally distributed at the 5% significance level (i.e. all P values < 0.05).

The ranges of set-up errors from normal distributions and histograms

Figure 4 shows histograms of the patient set-up error for each direction. The histograms in each of the coordinate axes spread monotonically. In the L–R direction, the spread of the histogram for the entire patient population of set-up errors was skewed to the left, showing higher error values. Similarly, the histograms were skewed to the superior or higher error values in the S–I direction and the anterior or higher error values in the A–P direction.

Table 1 shows the 95% CI_{norm} and the 95% RSE for different directions. For both the L–R and A–P directions, the 95% CI_{norm} was smaller than the corresponding 95% RSE. In the S–I direction, the 95% CI_{norm} was larger than the corresponding 95% RSE. The largest difference between the 95% RSE and 95% CI_{norm} was 1.28 mm in the S–I direction, while the smallest difference was –1.07 mm in the A–P direction.

DISCUSSION

Generally, patient set-up errors follow the central limit theorem. However, in this study, due to the small number of cases collected over a short time period, the error distributions of the patient set-up errors were not normally distributed. Our results indicate that the number of data points may be insufficient for the analysis of patient set-up error. In the L–R, S–I and A–P directions, the Q-Q plots were not linear. This non-linearity indicates that the error distributions are not normal distributions except for a very narrow interval. A difference between normal and observed set-up error was observed in both low and high set-up errors (Fig. 3). In addition, histograms were skewed to the right, superior and anterior for the L–R, S–I, and A–P directions, respectively (Fig. 4). The departure from normality is due to the set-up error variation from one patient to another, and so determining a representative value of patient set-up errors is difficult except for a very narrow interval. Therefore, more accurate patient set-up error correction is needed if patient set-up errors are assumed to follow a normal distribution.

These results take into account both the patient set-up error and the potential error caused by patient movement or organ motion during treatment. However, these separate

Table 1. Ranges of set-up errors that included 95% of all the patient set-up error data for each direction

	L–R	S–I	A–P
95% CI$_{norm}$ (mm)	5.53	39.28	14.13
95% RSE (mm)	6.10	38.00	15.20
Difference (mm)	−0.57	1.28	−1.07

95% RSE is the range of set-up errors that included 95% of the data from the histogram analysis. 95% CI$_{norm}$ is the range of the 95% confidence interval, assuming a normal distribution.

effects on the normality of the error distribution histograms were not determined. For set-up errors, the 95% CI$_{norm}$ was found to be smaller than the 95% RSE along the L–R and A–P directions. In the SI direction, the 95% CI$_{norm}$ was found to be larger than 95% RSE (Table 1). Therefore, making the assumption that set-up errors are normally distributed is not strictly valid. When assuming a normal distribution for the set-up error distribution for a small number of the clinical cases over a short data collection period, the applied margins on the PTV may result in an underestimate or an overestimate of the actual margins needed to account for patient set-up error. For example, in the L–R direction, an assumed normal distribution applies the same margin for both the left and the right sides of the CTV, even though actual set-up errors are different on each side. If this discrepancy is ignored, the actual dose distributions in the CTV and the nearby OARs will not be the same as those predicted during treatment planning, causing an underdosing of the CTV or an overdosing of the OARs.

Many researchers assume that patient set-up errors are normally distributed and have used these errors in determining margins applied to the PTV [1, 2, 3, 7, 9]. However, this study shows that patient set-up errors do not always follow a normal distribution. Therefore, we propose that when patient set-up errors are not normally distributed, these errors should be estimated using a range corresponding to the 2.5% and 97.5% interval of actual patient data histograms. Instead, margins applied to account for set-up errors following the recommendations of ICRU report 62 [10] may give a more accurate estimate of the needed set-up margin. In this way, the uncertainty in patient set-up margin analysis in radiation therapy can be reduced. Moreover, the latest advancements in image-guided radiotherapy (IGRT) integrate an in-room cone-beam computed tomography (CBCT) imager with radiotherapy linear accelerators for imaging on the day of treatment. CBCT images enable the radiotherapist to more precisely align patient position to the preplanned position. Images taken on the day of treatment allow changes in patient position, organ motion, and anatomical deformation that may take place over the course of radiotherapy to be measured and accounted for in order to improve the geometric accuracy

and precision of radiation delivery. The non-rigid alignment between the treatment planning CT and the repeat CBCT scans used for daily IGRT is a method for tracking complex organ motion on a voxel level. However, this is not an established method [11]. Therefore, the rigid alignment (i.e. bone base alignment) and this study are useful for IGRT from a statistical point of view.

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