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Reduction of prostate intrafractional motion from shortening the treatment time

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Abstract

This study aims to quantify the reduction of the intrafractional motion when the prostate IMRT treatment time is shortened. Prostate intrafractional motion data recorded by the Calypso system for 105 patients was analyzed. Statistical distributions of the prostate displacements for the regular IMRT treatment and the first 1, 2, 3 and 5 minutes of the treatment were calculated and used for treatment margin estimation for all the selected patients. The treatment margins estimated for the first 1, 2, 3 and 5 minutes were compared with those for the regular IMRT treatment to quantify the reduction of the motion. If the treatment can be completed within 5 (3) minutes, the standard deviation of the prostate displacement could be reduced by up to 45% and the required treatment margins could be reduced to 1.2 (1.1), 0.9 (0.8), 2.2 (1.9), 1.9 (1.5), 1.9 (1.7) and 2.8 (2.4) mm from 1.5, 1.1, 2.8, 3.0, 2.4 and 3.9 mm in the left, right, superior, inferior, anterior and posterior directions, respectively. Same work was also performed for 19 of the 105 patients who exhibited the largest motion with 30% of their treatment time having 3D motion more than 3mm. For this group of patients, the required margins change to 1.4 (1.2), 0.8 (0.8), 1.8 (1.6), 2.3 (1.8), 1.7 (1.5) and 3.4 (2.8) mm from 1.9, 1.2, 1.7, 3.7, 1.6 and 4.9 mm in the six directions when the treatment time is reduced to 5 (3) minutes. The intrafractional motion effects on prostate treatment are significantly smaller and the required margins can be therefore reduced when the treatment is shortened.

Summary—Prostate intrafractional motion was analyzed quantitatively based on the Calypso tracking data for the entire and the first 1, 2, 3 and 5 minutes of the prostate IMRT treatment. We found that shortening the treatment time can reduce the intrafraction motion and its effect and therefore it is possible to use a smaller margin for treatment. This finding tells that it is favorable to shorten the treatment time if the prostate motion can not be tracked.

Keywords

Prostate cancer; Intrafractional Motion; Treatment Margin

Introduction

Prostate intrafractional motion is one of the major concerns in external beam radiation therapy and studies have shown it can be significant for some patients (Langen and Jones, 2001; Huang *et al.*, 2002; Mah *et al.*, 2002; Aubry *et al.*, 2004; Britton *et al.*, 2005; Ghilezan *et al.*, 2005; Litzenberg *et al.*, 2006; Kotte *et al.*, 2007; Bittner *et al.*, 2010; Langen *et al.*, 2008). It is usually considered together with other geometrical uncertainties by adding a treatment margin to the clinical target volume (CTV) to ensure adequate dose coverage.

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However, adding a treatment margin will limit the degree of sparing of the nearby critical structures and normal tissues for treatment planning and therefore limit the degree of treatment-related complication reduction. Large treatment margins also prevent dose escalation because of the possible increase in normal tissue toxicity. Reducing geometrical uncertainties and subsequently reducing the treatment margins is the solution to these problems.

Interfractional motion or setup error can be reduced by improving the patient setup accuracy using the most advanced localization techniques, such as portal imaging with/without implanted fiducial markers (Balter *et al.*, 1995; Crook *et al.*, 1995; Millender *et al.*, 2004) and in-room CT, e.g. cone beam CT (Jaffray and Siewerdsen, 2000; Smitsmans *et al.*, 2005) or CT on rails (Court *et al.*, 2003; Paskalev *et al.*, 2004; Paskalev *et al.*, 2005; Ma and Paskalev, 2006; O'Daniel *et al.*, 2006; Feigenberg *et al.*, 2007). To reduce the intrafractional motion and its effects, real-time motion monitoring and tracking is required during the treatment. Four-dimensional (4D) localization systems, such as the fluoroscopic X-ray imaging system (Murphy *et al.*, 2001; Gerszten *et al.*, 2003) and the Calypso 4D localization system (Varian Med. Inc., Palo Alto, CA) with implanted electromagnetic transponders (Balter *et al.*, 2005; Willoughby *et al.*, 2006; Kupelian *et al.*, 2007; Li *et al.*, 2009; Langen *et al.*, 2008) are clinically available for this purpose. However, these systems may not be available for every treatment center because of the cost and the technique challenges (Byrne, 2005; Langen and Jones, 2001). Understanding the characteristics of the prostate intrafractional motion is still important and it may help on the motion control and therefore the reduction of its effects. The prostate intrafractional motion observed with the Calypso 4D localization system has been published by several groups (Kupelian *et al.*, 2007; Li *et al.*, 2009; Langen *et al.*, 2008; Li *et al.*, 2007; Bittner *et al.*, 2010). It has been concluded that the intrafractional motion could be significant for some patients and it could be irregular and unpredictable (Kupelian *et al.*, 2007; Langen *et al.*, 2008; Bittner *et al.*, 2010). Larger prostate displacements have been observed with a longer treatment time (Langen *et al.*, 2008; Bittner *et al.*, 2010). Therefore, shortening the treatment time could reduce the effect of intrafractional motion.

In this work, the prostate intrafractional motion recorded by Calypso systems was analyzed retrospectively. The correlation between the magnitudes of the prostate displacements from the base line with the treatment time was analyzed. The required treatment margins to compensate the intrafractional motion were calculated and used for quantitative comparison of the motion effect (Li *et al.*, 2009; Litzenberg *et al.*, 2006). The gains from shortening the treatment time for prostate treatment were evaluated based on the magnitude change of the intrafraction motion and the reduction of the calculated margin.

Methods and Materials

Prostate intrafractional motion recorded by the Calypso system

The Calypso 4D localization system with implanted electromagnetic transponders in the patient can continuously monitor the location of the tumour and the system is commercially available for prostate treatments. Three electromagnetic transponders are usually implanted in the patient prostate 10 days prior to the CT simulation and treatment planning. The correlation between the plan isocenter location and the three transponders' locations is determined based on the CT. During the patient setup procedure, the transponders will be detected by the Calypso transponder detection array which is put above the patient's abdomen and their locations in the treatment room coordinate system are determined. The plan isocenter location in the room coordinate system is then determined based on its relationship with the transponders. The perfect setup is to make the plan isocenter matching with the machine isocenter by moving the couch. During the treatment, the transponders'

location and thus the plan isocenter location is monitored by the Calypso system at a frequency of 10 Hz. The Calypso system reports and records the displacement of the isocenter in x, y and z directions every one tenth second. The recorded displacements of the isocenter during the treatment represent the intrafractional motion of the prostate. A 10-minute treatment will provide 6000 3-dimensional motion data points. These data points are collected in this study for intrafractional motion analysis.

Prostate intrafractional motion was observed and recorded with two Calypso 4D localization systems in our center. Statistical analysis of the prostate displacement in three directions was performed based on the data for the randomly selected 775 treatment fractions of 105 patients. The means and the standard deviations of the systematic errors and the standard deviations of the random errors for the prostate displacement during the treatment can be calculated along the three major dimensions for the entire regular IMRT treatment and some certain time periods during the treatment. The mean of the systematic error is the mean of the mean displacement of any individual patient. The standard deviation of the systematic error is the standard deviation of the mean displacement of any individual patient. The standard deviation of the random errors is the standard deviation of the prostate displacement for the patient population when the systematic error was removed. This statistical uncertainty calculation method has been used by many research groups for patient setup uncertainty calculation (Litzenberg *et al.*, 2002) and intrafractional motion analysis (Litzenberg *et al.*, 2006; Li *et al.*, 2009). Based on the measured motion data of a static phantom, the standard deviation of the Calypso system noise is less than 0.2 mm. Therefore, the noise of the Calypso system is ignored in the calculation.

Patient population-based margin calculation

Various methods have been proposed to define the impact of geometrical deviations on treatment margin and margin recipes have been derived by several research groups (Mageras *et al.*, 1999; Stroom *et al.*, 1999; van Herk *et al.*, 2000; van Herk *et al.*, 2002; Stroom and Heijmen, 2002). They have commonly concluded that a margin (m_{ptv}) for planning target volume (PTV) of 2 or 2.5 times the total standard deviation (SD) of the preparation (systematic) error plus 0.7 times the total SD of the execution (random) error is required. The one derived by van Herk *et al.* (van Herk *et al.*, 2002) based on coverage probability to ensure a minimum dose to the CTV of 95% for 90% of the patients is used in this study and it can be described as

$$m_{PTV}=2.5 \Sigma +0.7\sigma \quad (1)$$

where Σ is the total SD of systematic errors and σ is the total SD of random errors for a patient population. Σ and σ are quadratic sums of systematic errors and random errors of all the geometrical uncertainties, respectively. When the mean values of geometrical uncertainties are considered, it becomes

$$m_{PTV}=2.5 \Sigma +0.7\sigma+S \quad (2)$$

where S is the sum of the means of all the geometrical uncertainties.

Intrafractional motion for patients with different treatment time

Because this study focuses on the treatment time reduction and its impact on intrafractional motion, treatment time of regular IMRT treatment was analyzed first. The treatment time is the time between the completion of the initial setup and the completion of the treatment. It

includes the time for therapist to walk out of the room, to close the door, to load the treatment plan and the delivery of the treatment. There is not any imaging procedure involved. Every IMRT plan is specifically designed for a patient and the beam delivery time depends on the plan's complexity, the treatment time is therefore case dependent. Histogram of the treatment time distribution is plotted. The patients are also separated into different groups based on their treatment time. Statistical uncertainties of the intrafractional motion and then the required treatment margins were calculated for every individual group of patients. The results are used to demonstrate whether the patients with longer treatment time have larger intrafractional motion and thus bigger treatment margins.

Reduction of the intrafractional motion from shortening the treatment time

Because the prostate intrafractional motion is the major concern of this study, other geometry uncertainties are not considered in the margin calculation. The statistical intrafractional motion data, including the mean, standard deviation of the systematic error and random error, were calculated for the regular IMRT treatment for the entire patient population involved in this study. They were also calculated for the treatment time period of the first 1, 2, 3, and 5 minutes after the patient setup. The margins calculated based on these statistical motion data were compared to demonstrate the margin reduction by shortening the treatment time. In reality, the above mentioned intrafractional motion includes the residual setup error which is not perfectly zero in the routine clinic practice. The residual setup error is the first reading of the prostate displacement when the prostate motion is tracked by the Calypso system. Therefore, the required margins were also calculated based on this residual setup error and included in the comparison.

Based on the previous experience and the published literatures (Langen *et al.*, 2008; Li *et al.*, 2009), there is always a small group of patients have larger intrafractional motion than the others. This group of patients was distinguished in this study based on the percentage treatment time with motion in 3D more than 3mm and 30% was picked as the cutoff line. The intrafractional motion data of this group of patients was analyzed separately and the required treatment margins were calculated for the regular IMRT treatment and the first 3 and 5 minutes of the treatment. The gains on the treatment margin reduction when the treatment time is shortened were addressed. This group of patients are affected more by the intrafractional motion and therefore they could be benefited more from shortening the treatment time.

Results

IMRT treatment time distribution and the prostate intrafractional motion for patients with different treatment time

The step-and-shoot IMRT treatment time varies from 8.1 to 24 minutes for the selected 105 patients with 11.5 minutes as the median value. The distribution histogram of the treatment time per fraction is shown in Figure 1 in which the percentage of the patients having treatment time longer than a certain value (e.g. 100% of the patients having treatment time longer than 8.1 minutes and 60% of the patients having treatment time longer than 11 minutes) is indicated. The total treatment time for the IMRT is long and it could be shortened with the advanced treatment techniques such as the volumetric modulated arc therapy (VMAT and RapidArc) (Yu, 1995; Otto, 2008). The 105 patients were separated into 4 groups based on their mean treatment time per fraction, less than 9 minutes, from 9 to 11 minutes, from 11 to 13 minutes and more than 13 minutes. The statistical uncertainties of the intrafractional motion in the anterior-posterior direction are listed in Table 1 as an example. The negative mean value means the prostate towards to the posterior direction on average. This indicates the phenomenon of the prostate drifting to the posterior direction as

also reported by other researchers (Langen *et al.*, 2008; Bittner *et al.*, 2010). Comparing to the groups of patients with longer treatment time, the intrafractional motion as indicated by the mean, standard deviations of the systematic and random error is about 50% smaller for the group of patients with treatment time less than 9 minutes. For instance, the standard deviation of the systematic error is 0.38 mm for this group of patients versus 0.75 to 0.87 mm for other groups. The differences among other groups are small. The calculated margins in the six directions are shown in Figure 2 versus the average treatment time of each group. The results show that the required treatment margin is significantly smaller for the patient whose treatment time is less than 9 minutes in the posterior, anterior, inferior and superior directions. For patients whose treatment time is longer than 9 minutes, the required treatment margins are bigger but do not change significantly when the treatment time increases. This indicates that the magnitude of the intrafractional motion is saturated when the treatment is longer than 9 minutes.

Reduction of the intrafractional motion from shortening the treatment time for the entire patient population

Based on the recorded intrafractional motion data of the IMRT treatment, the statistical results of the motion along the three axes for all the selected cases are shown in Table 2. The means and the standard deviations of the systematic error and the random error for the regular IMRT treatment, the first 5 minutes (F5M) and the first 3 minutes (F3M) are compared in the table. Most of them become smaller when the treatment time is cut down, except for the mean value in the superior and inferior direction. The reduction is up to 45% comparing to the regular treatment, e.g. the systematic error in the superior-inferior direction. The negative mean value means the prostate towards to the right, the inferior and the posterior direction on average. The statistical results of motion for the first 2 minutes (F2M) and the first 1 minute (F1M) were also calculated and used for margin calculation. They were not shown in the table because of the limited space. Figure 3 illustrates the comparison of the calculated treatment margins in six directions based on the statistical results of motion shown in Table 2, and those for F2M, F1M and the residual setup error. The estimated treatment margins for the regular IMRT treatment are 1.5, 1.1, 2.8, 3.0, 2.4 and 3.9 mm in left, right, superior, inferior, anterior and posterior directions. If the treatment can be delivered within 5 minutes, the required treatment margins could be reduced to 1.2, 0.9, 2.2, 1.9, 1.9 and 2.8 mm, respectively, in the six directions. If the treatment time can be reduced to 3 minutes, the required treatment margins could be further reduced to 1.1, 0.8, 1.9, 1.5, 1.7 and 2.4 mm. From Figure 3, we can also observe that when the treatment time is further reduced to 2 minutes or 1 minute the intrafractional motion and the calculated margins have no significant change and they almost equal to those calculated based on the residual setup error. This indicates that the intrafractional motion is negligible when the treatment time is shorter than 2 minutes. The margin to cover the residual setup error is 1.0, 0.7, 1.5, 1.2, 1.6 and 2.0 mm in the left, right, superior, inferior, anterior and posterior directions, respectively.

Reduction of the intrafractional motion from shortening the treatment time for patients with large motion

Figure 4 shows the histogram distribution of patient number and the percentage treatment time with 3D motion more than 3mm. About 18.1% of the patients exhibit 3D motion more than 3mm for more than 30% of their treatment time. It means that 19 of the 105 patients exhibited the greatest intrafractional motion. The criteria of 3mm and 30% of the treatment time were taken subjectively in this study. However, the significant difference on the required treatment margin for this group of patients sets them apart. The statistical motion data derived based on the motion tracking data of these 19 patients are shown in Table 3. The calculated treatment margins based on this data for the regular IMRT treatment are

compared with those for the entire patient population in Figure 5. Significant bigger margins are required for this group of patients in the inferior and posterior directions. The bigger negative value of the mean in the superior-inferior direction and the anterior-posterior direction and the bigger margins indicate that this group of patients have more significant prostate drifting to the inferior and posterior directions during the treatment. The comparison of the required treatment margin of this group of patients for the regular IMRT treatment, the first 5 minute (F5M) and the first 3 minutes (F3M) is shown in Figure 6. The required margins change to 1.4, 0.8, 1.8, 2.3, 1.7 and 3.4 mm, or 1.2, 0.8, 1.6, 1.8, 1.5 and 2.8 mm from 1.9, 1.2, 1.7, 3.7, 1.6 and 4.9 mm in the six directions when the treatment can be completed within 5 or 3 minutes. The reductions of the margin sizes in the inferior and posterior directions are more significant than those in the other directions. Comparing to the entire patient population, the bigger margin reduction for this group of patients indicates that shortening the treatment time will benefit them more.

Discussion

It is still not possible to monitor the prostate motion and reduce its effects during every treatment in every cancer treatment center, therefore understanding the intrafractional motion is still very important and the adjustment on the treatment strategy based on the observed motion behavior could be beneficial for patient treatment. Less intrafractional motion was observed in this study in the first 5 minutes of the treatment. If the treatment time could be reduced to within 5 or 3 minutes, the treatment margin to cover the intrafractional margin could be reduced, especially for a small group of patients who have large motion during the treatment. Though a higher possibility to have a larger intrafractional motion with a longer treatment time has been observed by Langen et al. (Langen *et al.*, 2008) and Bittner et al. (Bittner *et al.*, 2010), quantitative analysis about the intrafractional motion reduction with the treatment time shortening has not been performed. Our study also indicates that the intrafractional motion has no further significant change after the treatment time is longer than 9 minutes.

A smaller treatment margin will benefit patient for normal tissue complication control. However, because the intrafractional motion is the only uncertainty considered for the margin calculation in this work, the reduction of the treatment margin in the clinic practice must be done cautiously. Other uncertainties were not included in the margin calculation because most of them are institution, observer and technique dependent, for instance, whether the magnet resonance images (MRI) are employed for target delineation will change the accuracy of contouring, and shortening the treatment time only affects the intrafractional motion.

The negative mean values of the prostate motion in the anterior-posterior and superior-inferior directions indicate the prostate drifting to the posterior and inferior direction on average during the treatment and this phenomenon has also been reported by other researchers (Langen *et al.*, 2008; Bittner *et al.*, 2010; Li *et al.*, 2009). The calculated margin reductions after shortening the treatment time are also more significant in these two directions. Therefore, the prostate drifting in these two directions requires bigger margins to ensure the dose coverage of the prostate if online motion monitoring is not available. However, a smaller margin is usually given in the posterior direction in the clinical practice in order to spare the rectum. This contradiction can certainly be alleviated by shortening the treatment time based on the results of this study.

Though the margin reduction is only 1.1mm in the posterior direction when the treatment time is shortened to 5 minutes based on the analysis for the entire patient population, the rectum dose and the normal tissue complication probability (NTCP) can be reduced

significantly based on a theoretical study (Li *et al.*, 2012). For the small group of patients, the posterior margin reductions are greater, 1.5mm for 5 minutes treatment time and 2.1mm for 3 minutes treatment time. Comparing to the current margin (3mm or 5mm in the posterior direction) used in the clinical practice for the prostate treatment, the reduction is significant. The equivalent uniform dose (EUD) of the rectum could be reduced by 5 to 10 Gy and the NTCP could be reduced from 13% to 2% with this margin reduction, based on the study on the relationship between the rectum NTCP and the prostate treatment margin (Li *et al.*, 2012). Shortening the treatment time is much helpful for some patients who have large intrafractional motion. More than 5mm motion has been observed during regular IMRT treatment for some patients (Balter *et al.*, 2005; Willoughby *et al.*, 2006; Kupelian *et al.*, 2007; Li *et al.*, 2009; Langen *et al.*, 2008).

New treatment technologies, such as the dynamic arc therapy (VMAT and RapidArc), provide us the ability to complete a conformal external beam treatment for prostate within a much shorter time. New computer-aided patient localization techniques and higher dose rate machine with faster gantry, collimator and multi-leaf collimator (MLC) leaf movement will help to reduce the treatment time as well. To localize the patient again in the middle of treatment based on the images or fiducial markers could also reduce the intrafractional motion effects if shortening the treatment time is not possible.

Conclusions

The intrafractional motion was analyzed quantitatively in this work by estimating the required treatment margin based on the recorded prostate intrafractional motion data. The magnitude of the intrafractional motion during prostate treatment becomes significantly smaller when treatment time is reduced to within 5 minutes. The required treatment margins to cover the intrafractional motion can also be reduced accordingly. The reduction is more significant for patient who has larger intrafractional motion than others and therefore they will be mostly benefited from the treatment time reduction. When the treatment time is reduced to within 2 minutes, no further significant reduction on motion is observed indicating that the intrafractional motion is negligible in the first 2 minutes. A minimum margin of 2 mm is required to cover the residual setup error in the posterior direction.

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Figure 1.
Histogram of the treatment time distribution for regular IMRT.

Figure 2.
Required treatment margin to cover the intrafractional motion for patient groups with different treatment time.

Figure 3.

Comparison of margins calculated based on the intrafractional motion data of the regular IMRT and the first 5, 3, 2, 1 minute of treatment and the residual setup errors for the entire patient population.

Figure 4.
Histogram of the percentage treatment time distribution with 3D motion > 3mm.

Figure 5.
Comparison of margins calculated for the regular IMRT treatment between the small group of patient and the entire patient population.

Figure 6.
Comparison margins calculated for the regular IMRT, the first 5 minutes and the first 3 minutes of the treatment for the small group of patient

Table 1

Statistical motion data including the mean (S), the standard deviation of systematic error (Σ) and random error (σ) and the required treatment margin in the anterior/posterior direction for different group of patient separated based on the length of their IMRT treatment time.

Treatment Time (Minutes)	< 9	9 to 11	11 to 13	> 13
Average Time (Minutes)	8.6	10.2	12.1	17.2
S (mm)	-0.32	-0.67	-0.75	-1.0
Σ (mm)	0.38	0.81	0.87	0.75
σ (mm)	0.36	0.97	0.94	0.94
Margin (mm)	0.9/1.5	2.0/3.4	2.1/3.6	1.5/3.6

Table 2
Statistical motion data including the mean (S), the standard deviation of systematic error (Σ) and random error (σ) of the entire patient population for the regular IMRT, the first 5 minutes (F5M) and the first 3 minutes (F3M) of the treatment

(mm)	Left-Right			Superior-Inferior			Anterior-Posterior		
	IMRT	F5M	F3M	IMRT	F5M	F3M	IMRT	F5M	F3M
S	0.20	0.18	0.17	-0.09	0.16	0.19	-0.75	-0.41	-0.33
Σ	0.34	0.26	0.23	0.77	0.51	0.42	0.80	0.59	0.5
σ	0.66	0.57	0.54	1.38	1.07	0.95	1.56	1.25	1.12

Table 3

Statistical motion data including the mean (S), the standard deviation of systematic error (Σ) and random error (σ) of a group of patient with the largest intrafractional motion for the regular IMRT, the first 5 minutes (F5M) and the first 3 minutes (F3M) of the treatment

(mm)	Left-Right			Superior-Inferior			Anterior-Posterior		
	IMRT	F5M	F3M	IMRT	F5M	F3M	IMRT	F5M	F3M
S	0.37	0.27	0.23	-1.01	-0.29	-0.11	-0.85	-0.41	-0.62
Σ	0.4	0.27	0.24	0.58	0.45	0.37	0.58	0.59	0.48
σ	0.8	0.62	0.57	1.74	1.32	1.16	1.60	1.25	1.40