INTRODUCTIO

Recent randomized studies for patients with localized prostate cancer confirm that improved biochemical failure-free survival was achieved by using higher doses of external beam radiotherapy (RT) (1–3). Although a higher dose is good for tumor control, it also carries greater risk of complications to surrounding critical structures, such as the bladder and rectum (4). Because of the inter- and intrafractional motion of the prostate, margin is required when planning a prostate radiotherapy. Knowing the extent of prostate movement during a fractionated, and more important a hypofractionated, treatment is necessary to reduce the treatment margin and facilitate prostate dose escalation (5, 6). A number of techniques have been developed for measuring setup variations and internal organ motion for individual patients from day-to-day and during a treatment fraction (7).

Ultrasound has been a useful tool for prostate target localization (8–10). Fung et al. (8) analyzed the data of 7,825 daily fractions of 234 prostate patients and indicated average three-dimensional (3D) interfractional displacement of about 7.8 mm. Electronic Portal Imaging Device, on-board kV X-ray imaging, or both of implanted fiducials is also widely used for initial setup and interfractional monitoring of the prostate target position (11–17). A recent development in measuring setup variations is the electromagnetic positioning and continuous monitoring system from Calypso Medical Technologies (Seattle, WA) (18–20). The difference between skin marks vs. the Calypso System alignment was found to be >5 mm in vector length in more than 75% of fractions. Displacements >3 mm and 5 mm for cumulative durations of at least 30 sec were observed during 41% and 15% of sessions, respectively. At our institution, CyberKnife (Accuray, Sunnyvale, CA) has been employed for Phase II hypofractionated treatment of prostate cancer. Through frequent stereoscopic X-ray imaging of implanted fiducials, the CyberKnife provides an effective way to monitor the position of the prostate target during a hypofractionated treatment (21). The system records the center of mass (CM) of implanted fiducials as computed
from each pair of stereoscopic images during each treatment, thus providing a valuable set of data to better understand the intrafractional movement of the prostate. In addition to the technical difference in monitoring the implanted fiducials, a major feature of our data is that the time span of tumor motion monitoring is significantly longer compared with the Calypso data (up to 2,500 sec with a mean duration of about 700 sec vs. 600 sec for Calypso). This study sheds useful insight into features of intrafractional prostate motion and reemphasizes the need for an effective means of compensating the intrafractional prostate movement to ensure adequate dose coverage of the tumor target.

**METHODS AND MATERIALS**

**CyberKnife data acquisition**

During hypofractionated prostate radiation treatment, fiducials must be rigidly fixed no more than 5–6 cm relative to a known reference or to the tumor. Any fiducial migration will degrade the accuracy of fiducial-based targeting. Commonly, three fiducials are used for prostate cancer treatment.

The patient setup and treatment delivery process is illustrated in Fig. 1. First, orthogonal X-ray images are acquired before treatment. The system determines the absolute position of the target volume via image-to-digitally reconstructed radiograph registration. The three-dimensional translation and rotation deviation of the target from the planned position is calculated. The deviation is corrected by manually moving the treatment couch. The treatment starts if the computed shift is less than a preset threshold, 10 mm in general. During treatment, the robot automatically adjusts the incident beam to compensate for the target deviation. The CyberKnife system can perform up to 10 mm translational correction. However, the larger the deviation, the greater is the uncertainty in the accuracy of the robot correction. Therefore it is recommended that the deviation during treatment be kept to a minimum. At Stanford Hospital, a threshold of ~5 mm translation is normally used. During the beam delivery, X-ray images are acquired every three nodes, which amounts to about a 40-sec interval. The shift of X-ray images from the planning CT is monitored in real time. If the calculated shift is more than the given threshold, the treatment will be paused, and manual couch movement is required until the shift is below the limit.

**Calculate shift ∆x**

- ∆x is more than threshold? [No]
  - Start treatment
- ∆x is more than threshold? [Yes]
  - Move couch
  - X-ray

**Patient selection and prostate motion data analysis**

The patients were treated with hypofractionated protocol consisting of five fractions of 7.25 Gy per fraction delivered every other day. In total, 21 prostate cancer patients were treated under the protocol between January 2005 and September 2007 for the study. In our analysis, one fraction can generate more than one data set because the treatment is usually paused a few times to reposition the patient by couch movement. The couch displacement is not kept in treatment log-file, and therefore the data sets before and after the intervening couch movement cannot be joined together without manually writing down the couch shifts during the treatment process.

**Fig. 1.** Flowchart of the patient setup and delivery process in CyberKnife treatment. DRR = digitally reconstructed radiograph.
After patient treatment, a log-file containing the CM displacements of the fiducials in anterior–posterior (AP), left–right (LR), and superior–inferior (SI) directions is saved in the CyberKnife control computer and can be readily used for the analysis of prostate movement during the beam delivery process. In addition, files containing the rigid body error (RBE) data of each implanted fiducial are recorded at each timestamp in the Accuray CyberKnife System. The RBE at a timestamp is defined as the distance of a fiducial from its corresponding CT position after the system figures out the best translation and rotation transformation by a rigid registration of the projection images and the CT-generated digitally reconstructed radiographs. For the 21 patients studied here, we first analyzed the statistical characteristics of the collected time duration data sets. This analysis provides valuable information on the average time it takes for the prostate to reach the preset threshold. The CM displacement log-files acquired during the treatment course were then studied and the overall and patient-specific behaviors of prostate displacement were investigated.

Study of prostate deformation

The RBE values mentioned earlier were employed to gain an understanding of prostate deformation. In general, the intrafractional motion of prostate consists of rigid and deformable motions. The rigid motion of the prostate is characterized by the CM displacement of the three implanted fiducials and any potential rotation. In principle, it is possible to estimate the prostate rotation on the basis of the angular change of the fiducial configuration. However, the prostate rotation is generally small and negligible. We have therefore focused our study on translation and deformable motions of the prostate. To a certain extent, the deformation can be described by the RBE values and the correlation between RBE curves of the three implanted fiducials. In an ideal case in which there is no deformation, the RBE should be zero, and the three time-dependent RBE curves would correlate completely. The correlation between three fiducials was computed for four representative cases.

Influence of X-ray image sampling rate

A clinically important question in stereoscopic image-guided prostate treatment is the optimal X-ray imaging frequency. Here the optimal imaging frequency is defined as the frequency that minimizes patient exposure while not missing any significant movement of the target during the beam-off interval of the imaging X-ray (22). To better understand the issue, we investigated the consequence of down-sampling the X-ray imaging data for one of the patients.

RESULTS

Duration of data sets

For the 21 patients, 4,439 timestamps, which constitute 427 separate data sets, were recorded. Figure 2 shows the histogram of the duration of the 427 data sets. The bin size is 200 sec, and the mean duration is 697 sec. The duration of a data set represents the time for the prostate to move beyond an acceptable level to the therapist (5 mm shift for prostate at our institution). Thus a shorter duration corresponds to a more prominent prostate movement. The data here suggest that on average it takes 697 sec for the prostate to move beyond 5 mm relative to its planned position.

Overall behavior of intrafractional prostate motion

A useful way to present prostate motion data is to show the histogram of the fiducial CM movement in different directions. As seen in Fig. 3, the prostate is more stable in the LR direction, which is consistent with pelvic and prostate anatomy. Generally, the shift distribution in the SI direction is similar to that in the AP direction. The mean shift in each direction, averaged over all patients, was 1.55 ± 1.28 mm,

<table>
<thead>
<tr>
<th>SI</th>
<th>LR</th>
<th>AP</th>
<th>Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.55</td>
<td>0.87</td>
<td>1.80</td>
<td>2.61</td>
</tr>
<tr>
<td>1.28</td>
<td>1.17</td>
<td>1.44</td>
<td>1.94</td>
</tr>
</tbody>
</table>

Abbreviations: AP = anterior–posterior; LR = left–right; SI = superior–inferior.
0.87 ± 1.17 mm, 1.80 ± 1.44 mm in SI, LR, and AP directions, respectively. The average vector length of the shift is 2.61 ± 1.94 mm. Table 1 summarizes the statistical characterization of the data for each direction and the vector length of the shift. It should be emphasized that these mean values were specific to the 5-mm threshold used in fiducial tracking because the greater-than-threshold shifts were reset by manual couch adjustments. It therefore does not represent the mean magnitude of prostate motion during a complete treatment fraction.

An alternative way to present the data in Fig. 3 is to illustrate the histogram of the prostate movement as a function of time duration and shift, as shown in Fig. 4. Each color represents a specific time segment. It is clear that as time elapses, the spatial distribution of the prostate becomes increasingly spread out. From these plots, it is also clear that SI and AP movements are similar, whereas the LR curve is more concentrative.

A rolling average (23) of total movement distance was computed in equal time-interval stamps to illustrate further the prostate movement tendency, as shown in Fig. 5. Because the average image acquisition interval is ~40 sec and using the Nyquist sampling theory (24), a time interval of 20 sec was used to calculate the rolling average curve. The rolling average window was set to be 120 sec. Thus the average shift at 0 sec is a result of shifts from 0 to 60 sec, and the average shift at 100 sec represents the contributions from 40 to 160 sec. Because there are not enough data for rolling average calculation at the end of the time duration, the calculation stopped at 1400 sec in Fig. 5. The curve in Fig. 5 represents

![Fig. 4. Histogram of the prostate movement as a function of time duration and shift.](image)

![Fig. 5. Rolling averages of prostate center of mass (CM) movement.](image)
Fig. 6. Patterns of prostate movement: (a) stable target at baseline, (b) continuous drift, (c) transient excursion, (d) persistent excursion, (e) high-frequency excursion, and (f) irregular movement (red: superior/inferior [SI] direction; green: left/right [LR] direction; blue: anterior/posterior [AP] direction; black: vector length of the shift).
a logarithmic fit of the data. It can be seen that the prostate movement increases against time.

**Patient-specific behavior of intrafractional prostate motion**

The motion of the CM of the three implanted fiducials is used as a surrogate of prostate motion. This quantity was recorded over time and analyzed for the 427 data sets (on average 20 data sets per patient). For illustration, a selection of six typical patterns of motion categories is shown in Fig. 6a–6f. The x axis represents the timestamp, and the y axis is the motion shift. Similar to those observed by Kupelian et al. (18), these patterns vary from stable positioning at baseline

![Prostate movement behaviors for one of the patients in different data sets](image)

Fig. 7. Prostate movement behaviors for one of the patients in different data sets (red: superior/inferior [SI] direction; green: left/right [LR] direction; blue: anterior/posterior [AP] direction; black: vector length of the shift).
(Fig. 6a), continuous drift (Fig. 6b), transient excursion (Fig. 6c), persistent excursion (Fig. 6d), and high-frequency excursion (Fig. 6e). Some patterns are simply too irregular to categorize into any of these classes (Fig. 6f).

It should be noted that for each patient, the prostate movement pattern may change from fraction to fraction or even from data set to data set within the same treatment fraction. Figure 7 shows the prostate movement behavior for one of the patients. This patient received five treatment fractions, and each fraction contains two data sets. Data sets 2, 4, and 5 are the continuous drift; data set 3 is the transient excursion; data sets 1, 7, and 8 consist of two continuous drifts; data sets 6 and 9 are high-frequency excursions followed by a stable positioning at baseline; and data set 10 shows a continuous drift followed by a stable positioning at baseline. These data suggest that the prostate intrafractional motion is somewhat random and does not follow a fixed pattern.

Influence of prostate deformation

Prostate deformation is of a practical concern. In Fig. 8, the RBE curves for each fiducial are plotted for four representative patients. The RBE value is generally within 1.5 mm, indicating that the deformation of the prostate is not a major issue here. Furthermore, as listed in Table 2, the correlation coefficients between RBE curves of the three implanted fiducials were found to be close to 100%. Although the fiducial movement profiles differ among patients, the motion behaviors of three fiducials for each patient are similar, indicating that no prominent deformation occurred in these cases.

Optimal image sampling rate

To understand the influence of the X-ray image sampling rate, we extracted a fraction of movement from one of the patients as shown in the solid line of Fig. 9a. Now suppose that the images are acquired at every other timestamp in the original acquisition schedule; the prostate movement curve would look quite different, as indicated in the dashed line of Fig. 9a. Figure 9b is another example of CM movement curve captured by two sampling rates. The peak in the solid curve revealed by a higher sampling rate disappears when the sampling rate is reduced. It is difficult to guarantee that there is no peak value in a relatively long sample interval. However, more frequent real-time imaging, which provides more accurate correction to the treatment robot, would result...
in longer treatment time and an increase in patients’ normal tissue dose.

In reality, a few factors may influence the selection of the sampling rate of the X-ray imaging, including the dose rate, patient-specific characteristics, the fractionation scheme, and so on. Therefore a trade-off between imaging frequency and target position accuracy must be made. A rule of thumb is that the movement of the prostate within the interval of two consecutive images should be less than a prespecified criterion, say 1 or 2 mm. Because of the randomness of prostate movement, this decision can only be made on a statistical basis. The sampling rate should be chosen in such a way that the number of data sets with displacement exceeding a prespecified motion range should be statistically small. Figure 10 shows a plot of the percentage for the prostate target to move more than 1 mm, 2 mm, 3 mm, 4 mm, 5 mm, ..., at 30 sec, 60 sec, 90 sec, 120 sec.... This figure is useful in helping to find the suitable sampling rate for a prespecified prostate motion range. For example, if motion greater than 2 mm is permissible for less than 5% of the data sets (in other words, if maintaining 95% of the data sets at a motion <2 mm is desirable), from Fig. 10, it is seen that a 30-sec sampling interval should be used. If a 60-sec interval is used, 7.5% of the data sets will have a motion greater than 2 mm. For 90-sec and 120-sec intervals, the percentage with motion greater than 2 mm will increase to 11% and 14%, respectively. For convenience, the percentage of data sets with motion greater than 1 mm to 5 mm is summarized in Table 3 for a few sampling intervals of interest.

**Table 2. Correlation coefficients between three fiducials for four representative cases**

<table>
<thead>
<tr>
<th>Fiducials</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 and 2</td>
<td>96.2%</td>
<td>97.7%</td>
<td>94.9%</td>
<td>97.8%</td>
</tr>
<tr>
<td>1 and 3</td>
<td>96.9%</td>
<td>98.2%</td>
<td>98.4%</td>
<td>99.2%</td>
</tr>
<tr>
<td>2 and 3</td>
<td>97.6%</td>
<td>97.0%</td>
<td>98.1%</td>
<td>98.8%</td>
</tr>
</tbody>
</table>

**DISCUSSION**

To cope with the uncertainty in patient setup and tumor target localization, a commonly used method is to add a population-based safety margin to the target and to sensitive...
adjacent structures to ensure adequate dose coverage, which significantly compromises the success of radiation therapy (25). Because of the proximity of the prostate to the rectum and bladder, a robust strategy in locating the tumor target is necessary if the radiation dose to the prostate is to be escalated to enhance the probability of curing patients without damaging adjacent structures. A detailed knowledge of prostate motion would help us to understand the nature and degree of the adverse influence of the uncertainty and provide guidance in dealing with this issue. The known motion patterns can also be included into inverse planning process to minimize its adverse dosimetric influence.

It is important to bear in mind that the proposed method relies on the assumption that the markers accurately reflect the position of the prostate. In other words, the implanted markers do not migrate significantly within the prostate during the course of treatment. Pouliot et al. (26) studied the issue by analyzing the orthogonal portal images of 11 patients. The distances between three markers were determined and monitored over the course of therapy to assess the magnitude of marker migration. The average standard deviation of the distances was found to be 1.3 mm. Similar observations were made by Poggi et al. (27), Nichol et al. (1), and Shirato et al. (28).

The prostate deformation study presented here is estimative in nature, primarily because the RBE and the correlation between RBE fiducial curves for each patient are less quantitative in assessing the organ deformation. However, it is a useful quantity and sheds practical insight onto the problem. A more thorough study based on biomechanical measures of the prostate deformation as a function of time is highly desirable to understand the issue completely.

There are several drawbacks associated with fiducial-based image-guided prostate radiation therapy. Other than the fact that it involves an invasive procedure of fiducial implantation, the fiducial tracking used with CyberKnife or the Calypso system is limited to "rigid" tumors. Although our data indicated that the deformation of the prostate gland during the hypofractionated treatment is small and the CM of the three implanted fiducials can be used to describe the prostate position, it is important to remember that tracking the prostate is only part of the overall task in prostate radiation therapy. In reality, tracking the motion of various adjacent sensitive structures represents the other side of the coin and is also

Fig. 9. Prostate movement behaviors depicted by stereoscopic imaging of two sample rates for two patients. (a) Patient 1, (b) Patient 2. CM = center of mass.

Fig. 10. Percentage of data sets for the prostate target as a function of sample interval and movement threshold.

<p>| Table 3. Percentage of data sets having a movement threshold from 1 to 5 mm for a few sampling intervals of interest |</p>
<table>
<thead>
<tr>
<th>Sampling interval</th>
<th>1 mm</th>
<th>2 mm</th>
<th>3 mm</th>
<th>4 mm</th>
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<td></td>
</tr>
<tr>
<td>30</td>
<td>10.5%</td>
<td>4.4%</td>
<td>2.3%</td>
<td>1.9%</td>
<td>1.2%</td>
</tr>
<tr>
<td>60</td>
<td>19.0%</td>
<td>7.5%</td>
<td>4.2%</td>
<td>3.2%</td>
<td>1.9%</td>
</tr>
<tr>
<td>90</td>
<td>30.2%</td>
<td>10.8%</td>
<td>6.6%</td>
<td>3.5%</td>
<td>2.6%</td>
</tr>
<tr>
<td>120</td>
<td>39.3%</td>
<td>13.8%</td>
<td>8.4%</td>
<td>4.9%</td>
<td>2.8%</td>
</tr>
</tbody>
</table>
of critical importance to the success of image-guided radiotherapy. Therefore, knowing the spatial location and geometric shapes of the sensitive structures is critical to customizing the dose distribution to maximize the dose to the target while sparing the adjacent sensitive structures. On a fundamental level, the motion of the prostate target is often caused by the motion or physiological change of sensitive structures.

This study, and most if not all similar studies, have focused on prostate-only treatment. Clinically, the treatment of intermediate- and high-risk prostate cancer often involves the irradiation of seminal vesicles and regional lymph nodes. The implanted fiducials in these cases are less helpful in locating the seminal vesicles and pelvic nodes. A better imaging method capable of providing three-dimensional anatomy would be highly desirable. On-board cone-beam CT (CBCT) has recently become available to provide volumetric information of a patient in the treatment position (29). It holds promises for improved target localization and irradiation dose verification (30). CBCT is valuable in providing 3D or even 4D patient model before treatment and affords a useful solution to reduce the adverse effect of interfractional organ motion (22, 31–34). However, acquiring real-time patient geometric information during radiation delivery using an on-boarding imaging device is still impractical. A combined use of pretreatment patient geometric model derived from 3D/4D CBCT and real-time stereoscopic X-ray projection data may be useful to estimate the location of target organs and adjacent sensitive structures. This investigation is still in progress and will be reported in the future.

CONCLUSION

Intrafractional organ motion has long been recognized as one of the major limiting factors of prostate dose escalation in conformal radiation therapy. A detailed knowledge of prostate motion would help us to understand the nature and degree of the adverse influence of such motion and provide guidance in dealing with it. Known motion patterns can also be included in the inverse planning process to minimize the adverse dosimetric influence of motion. Our study shows the importance of real-time image guidance and motion-compensation techniques such as the robotic linear accelerator used in CyberKnife during hypofractionated prostate radiation treatment. Given the magnitude and random nature of prostate motion as well as recent technical advancements in various related fields, real-time monitoring of prostate position to compensate for the motion should be part of future prostate radiation therapy to ensure adequate dose coverage of the target while maintaining adequate sparing of adjacent structures.

REFERENCES