Int. J. Radiation Oncology Biol. Phys., Vol. 61, No. 4, pp. 969–983, 2005

0360-3016/05/$–see front matter

doi:10.1016/j.ijrobp.2004.09.035

CLINICAL INVESTIGATION **Prostate**

APPLICATION OF THE NO ACTION LEVEL (NAL) PROTOCOL TO CORRECT FOR PROSTATE MOTION BASED ON ELECTRONIC PORTAL IMAGING OF IMPLANTED MARKERS

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Purpose: To evaluate the efficacy of the No Action Level (NAL) off-line correction protocol in the reduction of systematic prostate displacements as determined from electronic portal images (EPI) using implanted markers.
Methods and Materials: Four platinum markers, two near the apex and two near the base of the prostate, were implanted for localization purposes in patients who received fractionated high dose rate brachytherapy. During the following course of 25 fractions of external beam radiotherapy, the position of each marker relative to the corresponding position in digitally reconstructed radiographs (DRRs) was measured in EPI in 15 patients for on average 17 fractions per patient. These marker positions yield the composite displacements due to both setup error and internal prostate motion, relative to the planning computed tomography scan. As the NAL protocol is highly effective in reducing systematic errors (recurring each fraction) due to setup inaccuracy alone, we investigated its efficacy in reducing systematic composite displacements. The analysis was performed for the center of mass (COM) of the four markers, as well as for the cranial and caudal markers separately. Furthermore, the impact of prostate rotation on the achieved positioning accuracy was determined.
Results: In case of no setup corrections, the standard deviations of the systematic composite displacements of the COM were 3–4 mm in the craniocaudal and anterior-posterior directions, and 2 mm in the left-right direction. The corresponding SDs of the random displacements (interfraction fluctuations) were 2–3 mm in each direction. When applying a NAL protocol based on three initial treatment fractions, the SDs of the systematic COM displacements were reduced to 1–2 mm. Displacements at the cranial end of the prostate were slightly larger than at the caudal end, and quantitative analysis showed this originates from left-right axis rotations about the prostate apex. Further analysis revealed that significant time trends are present in these prostate rotations. No significant trends were observed for the prostate translations.
Conclusions: The NAL protocol based on marker positions in EPI halved the composite systematic displacements using only three imaged fractions per patient, and thus allowed for a significant reduction of planning margins. Although large rotations of the prostate, and time trends therein, were observed, the net impact on the measured displacements and on the accuracy obtained with NAL was small. **© 2005 Elsevier Inc.**

Organ motion, Portal imaging, Off-line verification, Fiducial markers.

INTRODUCTION

The geometrical uncertainties due to anatomy displacements during fractionated radiotherapy delivery may be classified according to two, intimately linked, decompositions. On the one hand, a distinction can be made between systematic and random displacements. The systematic component is, by definition, a patient-dependent constant displacement between treatment anatomy and planning computed tomography (CT) scan anatomy. This systematic component, which can be obtained for each patient by simply averaging the displacements observed in all treatment fractions, is largely because the planning CT scan, which defines the reference geometry, in fact captures an arbitrary random displacement (1, 2). The random component is the fluctuation around the systematic displacement (interfraction or intrafraction) and reflects that the displacements change over time. The distinction between a systematic (persistent) and random (fluctuating) component turns out to be crucial for the calculation of planning margins. It has been demonstrated that, to ensure dose homogeneity in the clinical target volume (CTV), systematic displacements require margins 3–4 times as large as random displacements

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Acknowledgments—The authors thank Joep Stroom for performing initial data analysis and useful discussions, as well as Petra van Kampen for her contribution to image registration.

Received April 26, 2004, and in revised form Sep 9, 2004. Accepted for publication Sep 16, 2004.

of comparable magnitude (3–5). Preliminary investigations indicate that systematic displacements play a similar important role when evaluating the influence of displacements on the dose to organs at risk (6, 7).

On the other hand, displacements relative to the planned irradiation geometry can be decomposed into internal organ motion and patient setup inaccuracies (for modern accelerator equipment, we may neglect the small inaccuracies in the shape of the delivered fields, in particular because they are taken into account to some extent in setup inaccuracies measured with electronic portal images (EPI) relative to the treatment field border). Setup inaccuracies are usually measured by the displacement of bony features. Because in many studies, patient setup is performed based on skin marks or marked fixation devices, the setup inaccuracies reflect the shift of the skeleton relative to these marks as well as the accuracy with which such marks can be aligned by eye to, e.g., treatment room lasers. Internal organ motion relative to the setup displacement can occur both on an interfraction and intrafraction basis. Both setup and internal organ motion are the cause of systematic and random displacements. However, for their impact on treatment margins, it is irrelevant whether systematic and random displacements are due to setup or internal organ displacements, as long as deformation of the target volume may be neglected (4). After all, the net systematic displacement is simply the addition of the systematic setup error and the systematic internal displacement, and the same holds for random displacements.

For prostate patients, the magnitude and nature of setup displacements has been studied extensively, partly because pelvic bones are usually well visible in EPI but also since the nearby critical organs (especially the rectum) demand a high positioning accuracy, particularly in dose escalation schedules (8, 9). Consequently, the statistical distributions of both systematic and random setup inaccuracies have been determined in large patient groups, and the prostate has been the primary treatment site for studies on the correction of the systematic setup inaccuracies through off-line correction protocols (10, 11). In general, an off-line correction strategy aims at estimating the systematic displacements based on a number of measured displacements in a given patient, usually obtained during the initial treatment fractions. Next, a decision is reached if, and by how much, the setup should be corrected in subsequent fractions. Because off-line corrections reduce systematic displacements, they can be effective in reducing treatment planning margins for the reasons pointed out above. In addition, they involve a substantially smaller workload than on-line protocols, which require daily imaging and preirradiation on-line image analysis. To achieve a significant reduction in margins for geometrical inaccuracies with a very small workload, we have proposed the No Action Level (NAL) protocol (11), which requires displacement measurements in only a few initial imaged fractions. We have shown both in detailed retrospective analyses as well as in prospective studies that this protocol can achieve an accuracy at least as good as previously applied off-line protocols while reducing the EPI-related workload by approximately a factor of 3 (11–14). This result has triggered other studies on the efficacy and optimum number of precorrection measurements of the NAL protocol in radiobiological and geometrical analysis (15, 16), which have yielded similar conclusions.

Studies on positioning corrections to reduce the composite displacement arising from both the setup inaccuracy as well as the prostate internal motion are very limited, primarily because the prostate motion can not be directly visualized on portal images. Transrectal ultrasound-guided implantation of prostate markers has in principle solved this problem (17–19). This approach has been used to study marker migration (20–22), prostate intrafraction motion (23–25), and the potential impact of marker-based setup corrections (26–29). Nevertheless, these studies have left a number of important questions open. First, in most studies that present prostate displacements measured with markers, no unambiguous description in terms of systematic and random displacements is given (17–19, 23, 24, 26–28). Such a separation is crucial to determine a proper off-line correction protocol and required planning margins (1). Similarly, rotations of the prostate, which have been observed to be significant in multiple CT scan studies (30, 31), have so far not been reported in sufficient detail in marker studies to assess their impact on correction strategies based on marker positions. Only one study (22) reported systematic and random components for rotations of the prostate, but in a small (<10) group of patients. The same group has published the only available study in which the effect of an off-line correction protocol based on marker displacements is quantified (29). However, in the "Discussion" section we point out that the drawbacks of the protocol they have chosen render clinical implementation unpractical.

We conclude that, to date, no quantitative description of the positioning accuracy of the prostate, attainable with a specific, well-validated, and practically attractive off-line correction protocol has been presented. Consequently, the potential gain in planning margins achievable by off-line corrections has not been satisfactorily assessed. As mentioned above, the NAL protocol has been shown to be effective and efficient in the reduction of systematic patient setup errors (bony anatomy). This article aims at a reliable quantification of the efficacy of the NAL protocol in the reduction of composite systematic prostate displacements (bony anatomy plus internal prostate motion), based on measured displacements of fiducial markers in EPI.

Because markers were placed both near the base and the apex in each patient, the motion of these regions could be studied separately, and rotation of the prostate could be separated from translation. These results were used to determine residue errors if displacements are corrected based on the center of mass position of all markers. Furthermore, we performed a time trend analysis on prostate motion with a much better time resolution than multiple CT studies. This is of importance because such trends could have a detrimental effect on the outcome of off-line protocols.