

Evaluation of Interfractional Movement of the Seminal Vesicle and Dose Variations with IGRT Throughout the Prostate Cancer Radiotherapy

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ABSTRACT

To validate the actual cumulative doses delivered to the seminal vesicle (SV) depending on the organ movement using kV-Cone Beam CT (kV-CBCT) datasets acquired during prostate image-guided radiation therapy. Ten patients with intermediate risk prostate cancer treated with IMRT were included in this study. Both the prostate and the first 2 cm of the SV were included in the CTV. PTV margin was 8 mm in all directions except posterior, where it was 5 mm. Sixteen kV-CBCT scans per patient were used for assessments. After each kV-CBCT was matched with the planning CT based on prostate, the SV were recontoured as proximal, distal SV and both of them together (the whole SV). Actual delivered doses to the SV were assessed by means of DVH. The variations in certain dose-volume parameters were analyzed using the Student's test. Systematic and random errors of the SV and margins were assessed using the van-Herk formula. We observed that the SV movement in the anterior-posterior direction was significantly more compared to superior-inferior and left-right direction. The dose volume variations for the whole SV (D98%, D50%, D2%) and the distal SV (D98%, D95%, D50%) were significantly different than the planned doses. However, both the whole SV and the distal SV received the prescribed dose. Although it seems that there is a need to give larger margin to the SV in posterior direction, the actual cumulative doses delivered to SV throughout the treatment were within the prescribed dose.

Keywords: Image guided radiation therapy, Interfraction motions, kV-CBCT, Prostate cancer, Seminal vesicle

ÖZET

Prostat kanseri Radyoterapisi Sırasında Fraksiyonlar Arası Seminal Vezikül Hareketleri ve Doz Değişimlerinin IGRT ile Değerlendirilmesi

Bu çalışmanın amacı, kV-Cone Beam CT (kV-CBCT) ile görüntü kılavuzluğunda prostat kanseri radyoterapisinde organ hareketine bağlı olarak seminal veziküllerin aldığı kümülatif dozların doğruluğunun değerlendirilmesidir. Çalışmamıza IMRT tekniği ile tedavi edilmiş orta risk prostat kanserli on hasta dahil edilmiştir. Prostat ve seminal veziküllerin ilk 2 cm'lik bölümü CTV'ye dahil edilmiştir. Prostat ve SV'e posterior yönden 5 mm, diğer yönlerden 8 mm PTV marjı verilmiştir. Her hastadan 16 kV-CBCT alınmış ve SV'ye verilen marjın yeterli olup olmadığını saptamak için seçilen kV-CBCT görüntüleri ile planlama BT görüntüleri prostat referans alınarak offline eşleştirilmiştir. Seminal veziküller, proksimal-distal SV şeklinde ayrı ayrı ve her ikisi birlikte tüm SV olacak şekilde yeniden konturlanmıştır. Seminal veziküllerin aldığı doz DVH yardımı ile değerlendirilmiştir. Doz volüm histogramındaki değişiklikler Student test ile analiz edilmiştir. Sistemik ve random hatalar van-Herk formülü ile değerlendirilerek gerekli emniyet marjları bulunmuştur. Seminal vezikül hareketinin alt-üst ve sağ-sol yöne kıyasla ön-arka ekseninde daha fazla olduğu görülmüştür. Tüm SV için (D98% D50,% D2%) ve distal SV için doz volüm değişiklikleri (D98% D95,% D50%) planlanan dozlardan önemli ölçüde farklı bulunmuştur. Bununla birlikte, tüm SV ve distal SV'in tanımlanan dozu aldığı tespit edilmiştir. Çalışmamıza göre PTV marjının posterior yönde daha fazla olması gerektiği görülmesine rağmen, tedavi boyunca verilen dozlara kümülatif olarak bakıldığında SV'ler tanımlanan dozu aldığı için posterior marjin değerlerinde herhangi bir değişikliğe gidilmemiştir.

Anahtar Kelimeler: Görüntü kılavuzluğunda radyoterapi, Fraksiyonlar arası hareket, kV-CBCT, Prostat kanseri, Seminal vezikül

INTRODUCTION

Intensity modulated radiotherapy (IMRT) technique improved both local and biochemical control and treatment related toxicity in the treatment of prostate cancer compared to 3-dimensional conformal radiotherapy.¹⁻⁵ Therefore, a high dose of IMRT as the standard treatment for early and locally advanced prostate cancer has been recommended recently. For patients with intermediate and high risk prostate cancer, seminal vesicles (SV) have a higher risk of invasion and are recommended to be included to the clinical target volume (CTV).⁶⁻⁷ However, the prostate and SV may be subject to inter- and intrafractional motions because of the changes in rectal and bladder filling. These displacements are important when treating prostate and SV with simultaneous IMRT irradiation technique due to the sharp dose gradients. Image guided radiotherapy (IGRT) is used to eliminate these inter- and intrafraction organ variations and set-up uncertainties during radiotherapy.⁸⁻⁹

In the literature, the prostate motion has been well described while SV motion and dosimetric analysis have been relatively less well reported.¹⁰⁻¹⁸ When the SV are included in the target volume, independent motion and the rotation of the SV and prostate may affect the dose distribution of the SV in prostate based image guidance. Stenmark et al. showed that the displacement of the SV was different from the prostate and this movement was more in the distal part rather than the proximal part of SV.¹⁸ Although the majority of the studies analyzed the inter- or intrafraction displacements of the SV and the planning target volume (PTV) margins, there is little data about the cumulative dose distribution of SV throughout the treatment.¹⁵⁻¹⁸

In this study is aimed to validate the actual doses delivered to the seminal vesicle depending on the organ movement by IGRT methods.

PATIENTS AND METHODS

Simulation and Planning

Ten consecutive patients with intermediate-risk prostate cancer treated radically with IMRT technique were included in this study and 16 kV-CBCT for each patient were retrospectively evaluated. According to our institutional protocol, patients were asked to use a low-fiber diet and mild laxa-

tives starting one week before the planning CT scan and during radiotherapy. In consultation with the radiation oncologist, the dose of laxative could be adjusted. They were asked to come to the department with an empty bladder and rectum and to drink 500 ml of water 30 minutes prior to the simulation and each treatment session. The bladder volumes were checked by ultrasonography before planning CT and each treatment. These patients were positioned in supine position on a couch and immobilized with knee and foot supports. Planning computerized tomography scan (CT) of patients was taken from the level of the third lumbar vertebrae to the middle of the femurs on a G.E. Lightspeed 16 CT scanner (General Electric Healthcare, Waukesha, WI) using a slice thickness of 2.5 mm. Volume delineations were manually contoured by a single radiation oncologist. The prostate and the proximal 2 cm section of the SV from the prostate-SV junction were considered CTV. Planning target volume was generated from the prostate and SV using expansion margins of 8 mm in all directions except posterior, where it was 5 mm. All of the treatments were planned with either a dynamic IMRT or a VMAT technique and optimized using the Eclipse version 8.6 treatment planning system. The doses to the planning target volumes of prostate and seminal vesicles in 39 fractions of 78 Gy and 56-58 Gy, respectively and delivered with a simultaneous boost technique.

Treatment

All patients were treated for 5 consecutive weekdays on an integrated CT-LINAC system (Varian Clinac® IX model, Varian Medical Systems, Palo Alto, CA). Target localization was performed based on the prostate matching using daily half-fan (40x35cm) kV-CBCT scans before each treatment. Bladder and rectum volumes on the CBCT were compared with the CT simulation scan and were assessed by the same physician. When there is deformation of the prostate due to rectal fullness, the patients were taken off the couch and asked to empty their bowel. Then again, the bladder and rectum preparation was done and treatment setup procedure was repeated from the beginning.

Alignment of kV-CBCT with planning CT images based on prostate and interpretation of images was

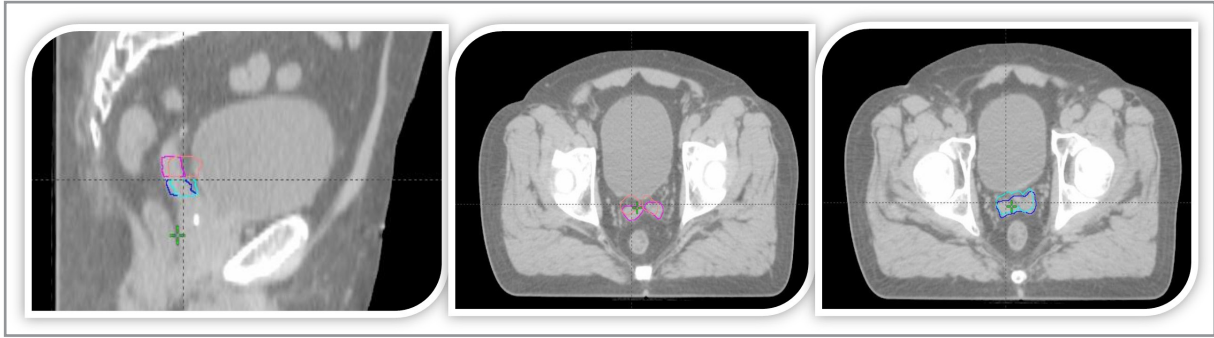


Figure 1. SV deformations projected on planning CT scan (Pink: distal SV on planning CT scan; Blue: proximal SV on planning CT scan, Orange: distal SV on at fraction 7, patients 8; Cyan: proximal SV on at fraction 7, patients 8)

done by the same physician for all patients to eliminate interobserver variability.

Data Collection and Analysis

In this study, 16 kV-CBCTs which were taken at the first five days of treatment and then two times per week for each patient were used for assessments. After each kV-CBCT images matched with the planning CT images based on the prostate, SV were re-contoured in three different parts: the first 1 cm of SV from the prostate-SV junction as proximal (p), second 1 cm from the prostate-SV junction as distal (d) and both of them as a whole (w) SV on planning CT images by the same physician. For the analysis, first we matched kV-CBCT scans with CT scan based on whole SV in off-line in order to assess the PTV margin for SV. Systematic (Σ) and random (σ) errors of SV and margins were assessed using the van Herk formula $[2,5\Sigma+0,7\sigma]$.

Later, offline kV-CBCT images were matched with the planning CT based on prostate and the delivered doses were assessed with dose volume histograms (DVH).

The variations in certain dose-volume parameters of the proximal, distal parts of SV and the whole SV (D98%, D95%, D50%, D2%, D max) were analyzed using Student's test.

According to national rules do not require obtaining ethical committee approval for retrospective studies. Before the analysis our institutional board was informed that this study was conducted in accordance with the principles of Helsinki declaration and the rules of Good Clinical Practice.

RESULTS

We evaluated a total of 160 kV-CBCT scans and 480 corrected patient's data sets.

Table.1. The systematic and random errors for seminal vesicle.

	Seminal vesicle		
	Mean	SD**	Range
Systematic interval variation (cm)*			
AP (antero-posterior)	0.11	0.17	-0.29 to 0.33
SI (superior-inferior)	-0.04	0.16	-0.30 to 0.30
LR (left-right)	-0.02	0.13	-0.18 to 0.33
Random interval variation (cm)			
AP (antero-posterior)	0,38	0,07	-0,1 to 0,21
SI (superior-inferior)	0,25	0,05	-0,12 to 0,1
LR (left-right)	0,27	0,04	-0,1 to 0,1

(* cm: centimeter, ** SD : standart deviation)

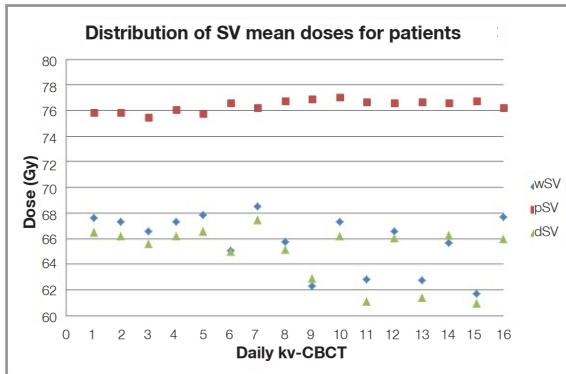


Figure 2. The distribution of mean doses of whole, proximal and the distal SV in patient 8 throughout the treatment

The interfraction displacement (\pm SD) was 0.38 ± 0.07 cm in anterior-posterior (AP), 0.25 ± 0.05 cm superior-inferior (SI) and 0.27 ± 0.04 cm in left-right (LR) axis. We observed that the movement in the anterior-posterior direction was significantly more compared to superior-inferior and left-right direction (Figure 1). In addition, the rotation of the SV was determined less than 0.5 degrees (mean 0.01 ± 0.03^0) in all patients. The systematic and the random errors for the SV are shown in Table 1.

The PTV margin of the SV according to van Herk formula was found to be 0.68 cm for anterior-posterior, 0.58 cm for superior-inferior and 0.50 cm for lateral directions. The dose volume variations for the whole SV (D98%, D50%, D2%) and the distal SV (D98%, D95%, D50%) were significantly different than the planned doses ($p < 0.05$) while there was no statistically significant difference in doses of proximal SV (Table 2). However, both the whole SV and the proximal and the distal SV received the prescribed dose. The distribution of mean doses of the whole, proximal and the distal SV throughout the treatment in one patient are shown in Figure 2.

DISCUSSION

In the present study, we investigated the interfractional motion of SV and the influence of this movement on the actual doses delivered to SV in intermediate-risk prostate cancer patients, using kv-CBCT data sets. SV are usually included in the CTV for the treatment in intermediate-risk and high-risk prostate cancer patients. We delineate the first 2 cm portion of the SV from the prostate-SV junction as a CTV; we do not include the whole SV in the CTV which will be translated to higher

Table.2. Comparisons of planned and actual doses to the whole, proximal and distal seminal vesicle (SV).

	Planning dose (Gy)	Actual dose (Gy)	95 % Confidence interval		p
			upper	lower	
Whole SV					
Dmax	82.11	81.99	-0.2698	0.0265	0.107
Mean	74.15	73.63	-0.879	-0.176	0.003
D98%	63.44	62.80	-1.267	-0.006	0.048
D95 %	64.98	64.50	-1.098	0.128	0.121
D2 %	81.30	81.12	-0.349	-0.004	0.044
Proximal SV					
Dmax.	81.98	81.91	-0.243	0.098	0.403
Mean	77.82	77.40	-1.356	0.522	0.382
D98%	71.59	71.20	-0.995	0.208	0.199
D95 %	72.77	72.65	-0.669	0.416	0.645
D2 %	81.24	81.21	-0.244	0.173	0.700
Distal SV					
Dmax.	76.83	76.91	-0.250	0.405	0.642
Mean	70.28	69.89	-0.780	-0.011	0.044
D98%	63.93	63.20	-1.323	-0.125	0.018
D95 %	65.02	63.37	-1.212	-0.099	0.021
D2 %	75.45	75.32	-0.472	0.212	0.455

doses to the normal tissues. There is limited data about the extension of tumor invasion for the SV. The only detailed data showing the risk of invasion of the SV was reported by Kestin et al.⁶ They made a histopathological evaluation of 334 radical prostatectomy specimens and found that the risk of finding tumor cells was 7% beyond 1cm and 1% beyond 2 cm from the prostate-SV junction for the entire population. For the 81 patients with SV involvement, this rate was 41% beyond 1 cm and 6% beyond 2.0 cm, 1% beyond 3 cm from the junction and they concluded that only proximal 2.0-2.5 cm of the SV should be included during prostate irradiation.⁶ In daily practice the extension of the delineation of the SV changes from center to center. Some centers prefer to include all of the SV in the CTV while some of them includes the proximal 2.0 cm of the SV.¹⁵⁻¹⁶

Currently, interfraction displacement of the prostate and SV is demonstrated with various IGRT methods. Some authors noted that the SV move independently from the prostate and more than the prostate and they suggested to give larger margins.^{16,18,19} In addition, Stenmark et al. reported that the SV motion was increasing towards the distal part.²⁰ Mak et al. performed a geometric analysis both for the right and the left SV and reported that >15 mm margins are needed to cover the entire left and right SV on at least 90% fractions for 90% of the patients.²¹ Whereas, Meijer et.al found at least 8 mm margin should be given for SV.¹⁵ In most of these studies, daily fiducial marker based set-up corrections had been done and the target margin had been evaluated according to the prostate movement.^{12,14,16}

In this study, we found that the SV motion was significantly more in the AP axis and the distal part of SV. At least 7 mm PTV margin was required in the posterior direction. The movement of the SV in SI, lateral directions was in the limits of our PTV margins. Mutanga et. al reported that displacements of the SV were mostly related to the deformations due to bladder and rectal filling, therefore, it is not appropriate to consider the displacements as geometrical rigid motions.¹⁶

There are few studies examining the effect of the deformation of the prostate and SV on the dose distribution.^{15,16,18} Therefore, we analyzed the dose

changes and the cumulative dose to the SV throughout the radiotherapy which may be more realistic and superior than the rigid motion assumptions. We found that the dose volume variations for the whole SV and the distal SV were significantly different than the planned doses. However, the whole SV and proximal and distal SV doses were within the prescribed doses. This might be due to the contribution of the dose from the superior part of the prostate to the dose to the SV.

It has been shown that, the geometric and volumetric displacement of the prostate and SV is correlated with the bladder and rectum filling and intestinal motility.²²⁻²⁷ In addition, most of the studies concluded that the displacement of SV is more than prostate. Online and offline corrections are helpful to eliminate set-up uncertainties and to reduce systematic errors.^{23,28,29} In the present study, both the systematic and the random errors for SV and rotation values were relatively lower than the other reports. This may be due to the fact that we follow a strict bladder and rectum preparation protocol before the planning CT and during the treatment course. Some studies have noted that dietary recommendations, rectal preparation and bladder filling protocols in prostate radiotherapy could decrease the interfractional variations.²⁶⁻²⁷ Similarly, we showed that the similar protocols minimize the variations in displacement and deformation of prostate bed, bladder, and rectum with daily kV-CBCT IGRT.³⁰

Gill et al. investigated SV motion with cinematic magnetic resonance imaging in real time. To our knowledge, that was the first article presenting the real-time intrafractional motion of the SV. They demonstrated that the displacement of the SV was increased during treatment and was more in the superior-inferior direction. They recommended giving an additional margin to the SV if the dose is delivered based on the prostate. But the dose changes of the SV during the course of radiotherapy has not been analyzed.¹⁹ In our study, the intrafraction motion was not taken into account while most of our patients were treated with the VMAT technique, which is faster than the dynamic or static IMRT.

There are some limitations to our study. Although the same physician performed the off-line matching based on prostate and contoured SV, there

might be mismatching due to uncertainty of the margins of the prostate and contouring variations on the CBCT images used for this analysis. The positional and volumetric changes or deformations in SV are compensated by PTV margins. We analyzed these changes in x,y,z directions and performed dosimetric effect of interfractional motion in IMRT. On the other hand, we did not evaluate the geometric uncertainties which may give additional information.^{22,23}

In conclusion, our findings indicate that the posterior margin of the SV was insufficient to cover motion and deformation during simultaneous irradiation of the prostate and SV. However, the SV received the prescribed dose when we reviewed the cumulative DVHs. So that received dose of the seminal vesicles during the treatment has been validated. Therefore, there is no need to give relatively large margin in posterior direction. We believe that, daily IGRT with CBCT and well instructed and controlled bladder and rectum preparation facilitate to irradiate patients safely with smaller margins. However, inter-intrafractional movements should be always kept in mind, and departments should assess their margins in order to determine their own protocols.

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