Scientific Paper

Determination of the CTV-PTV margin for prostate cancer radiotherapy depending on the prostate gland positioning control method

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Abstract

Objective: The objective of the study was to determine the correct CTV-PTV margin, depending on the method used to verify the PG position. In the study, 3 methods of CBCT image superimposition were assessed as based on the location of the prostate gland (CBCT images), a single gold marker, and pubic symphysis respectively.

Materials and methods: The study group consisted of 30 patients undergoing irradiation therapy at the University Hospital in Zielona Góra. The therapy was delivered using the VMAT (Volumetric Modulated Arc Therapy) protocol. CBCT image-based superimposition (prostate-based alignment) was chosen as the reference method. The uncertainty of the PG positioning method was determined and the margin to be used was determined for the CBCT-based reference method. Then, changes in the position of the prostate gland relative to these determined using the single marker and pubic symphysis-based methods were determined. The CTV-PTV margin was calculated at the root of the sum of the squares for the doubled value of method uncertainty for the CBCT image-based alignment method and the value of the difference between the locations of planned and actual isocenters as determined using the method of interest and the CBCT-based alignment method for which the total number of differences accounted for 95% of all differences.

Results: The CTV-PTV margins to be used when the prostate gland is positioned using the CBCT imaging, single marker, and pubic symphysis-based methods were determined. For the CBCT-based method, the following values were obtained for the Vrt, Lng, and Lat directions respectively: 0.43 cm, 0.48 cm, 0.29 cm. For the single marker-based method, the respective values were 0.7 cm, 0.88 cm, and 0.44 cm whereas for the pubic symphysis-based method these were 0.65 cm, 0.76 cm, and 0.46 cm.

Conclusions: Regardless of the method, the smallest margin values were obtained for the lateral direction, with the CBCT-based method facilitating the smallest margins to be used. The largest margins were obtained using the single marker-based alignment method.

Key words: prostate; CTV-PTV margin; marker; positioning control.

Introduction

Prostate gland (PG) cancer is the most commonly diagnosed cancer in men.^{1,11,12} Basic treatment modalities include radical prostatectomy or radiation therapy (teletherapy and brachytherapy).^{2,13-16} Teletherapy makes use of state-of-the-art conformal techniques, namely the intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT).^{5,20} PG is an organ characterized by significant internal mobility.^{3,8} Its movements are observed primarily in the superoinferior and anteroposterior directions.⁹ Due to the mobility of the PG, the delivery of a full therapeutic dose requires that the position of the prostate is monitored along with the position of the pelvic isocenter.³ Several methods are available for the measurement of the position of PG relative to the isocenter. One of such methods consists of a cone-beam computed tomography (CBCT) scan being acquired

immediately before each treatment session.¹⁶ Due to the low contrast between the PG and the surrounding tissues, determination of the prostate's position relative to the bone structures is difficult and quite time-consuming. A better method to increase the precision of PG positioning consists of the use of prostate-implanted fiducial markers.²⁰ The markers, made of high-Z material, are clearly visible in kilovolt imaging,⁴ facilitating relatively quick and easy determination of PG position relative to the radiotherapy apparatus isocenter. High-quality treatment requires that rectal and bladder filling levels are monitored, as they affect the position of PG relative to the bone structures. Therefore, rectal voiding is recommended at numerous radiotherapy centers prior to each irradiation;^{6,17} patients are also asked to drink a certain volume of water at a specified time before irradiation.^{6,17} The same rules apply before treatment-planning tomography is

performed. This improves the reproducibility of patient anatomy. No matter how advanced are the implemented methods to ensure the reproducibility of patient anatomy, the Clinical Target Volume to Planning Target Volume (CTV-PTV) margin value should be taken into account in order to deliver the full therapeutic dose.^{21,22} Protection of critical organs requires that the margin be minimized. A number of studies were published to present a wide overview of CTV-PTV margin values depending on many factors, i.e., imaging frequency, imaging type (CBCT vs portal scans), radiotherapeutic technique, patient preparation protocol, and, most importantly, the alignment control method.⁷ A margin of 10 mm or larger should be added when the patient is positioned in relation to their tattoos or bones. A CTV-PTV margin of 5–8 mm can be used for everyday imaging on the basis of soft tissue alignment (CBCT imaging). Slightly smaller margins can be used when the position of the PG is determined by means of fiducial markers. The smallest margins, as small as 3 mm, can be used when the prostate position is determined in real-time using transponders and adaptive imaging techniques are being used to obtain the scan.^{7,9} The margin size should match the capabilities of the radiation treatment unit.

The objective of this study was to determine the CTV-PTV margin size depending on the patient alignment protocol. Margins were determined for 3 different techniques: CBCT-based alignment, a single gold marker seed-based alignment, and pubic symphysis-based alignment.

Materials and methods

Patients

The study group consisted of 30 patients receiving radiation therapy for prostate cancer (T1–T3) at the K. Marcinkowski University Hospital in Zielona Góra. The age of the patients was 72 years; the median PSA value was 22 ng/mL (5.2–93 ng/mL) while the median Gleason score was 7 (6–9).²⁶ Ten patients were classified as being at moderate risk of recurrence, whereas 14 and 6 patients were classified into groups of the high and very high risk of recurrence, respectively. In three patients, the treatment was combined with brachytherapy whereas 4 patients were treated using a hypofractionation regimen. Patients with a mean survival of more than 10 years and being at high or very high risk of recurrence were treated using a dual- or triple-stage regimen involving the lymph nodes. Patients at high and very high risk of recurrence and having a mean survival of fewer than 10 years were treated using a single- or dual-stage regimen depending on local tumor grade whereas patients with a moderate risk of recurrence were treated using a single-stage regimen.²⁷

Irradiation technique

One fiducial gold marker was implanted into the bulk of each patient's prostate gland prior to direct preparation to radiation therapy. After approximately two weeks, a treatment planning

spiral CT scan was acquired; patients were instructed to void their bowels and drink 3 to 4 glasses of water 45 minutes before the study. Patients were placed in a supine position with knee support. Tattoo alignment markings were placed on each patient's skin, including two lateral markings and one pubic symphysis marking. CT scans reconstructed every 3 mm were sent to a Varian ARIA system where the outlines of the bladder, rectum, femoral bones, fiducial marker, and treatment volumes (CTV and PTV) were plotted onto the scans. Depending on the disease grade, the CTV included the lymph nodes, the seminal vesicles, and the prostate gland. Margins of 0.5 cm were added to the CTV (prostate and seminal vesicles) outlines. Then, volumetric modulated arc therapy (VMAT) plans were developed by medical physicists using the Eclipse v. 13.6 system. The treatment plans have been made with the SAD technique with the treatment isocentre in the center of the target area. The treatment isocenter is represented by the accelerator mechanical isocenter which is defined as the intersection of the central axis of the beam with the axis of rotation of the gantry, while the visual representation of the mechanical isocenter is the intersection of the lasers (sagittal and lateral) located in the bunker. The IGRT technique relies primarily on enhanced image control. The QA (Quality Assurance) of the imaging system is very important and above all the control of the convergence of the imaging isocentre with the treatment isocentre and thus with the accelerator mechanical isocentre. Depending on the disease grade, the therapy was delivered in one, two, or three stages. For patients treated with teleradiotherapy alone, the total dose was 70.2–78 Gy in fractionated doses of 2 Gy or 2.7 Gy and was calculated against the ICRU reference point, whereas in patients receiving teleradiotherapy in combination with brachytherapy, the treatment regimen consisted of 50 Gy administered in fractionated doses of 2 Gy as a part of teleradiotherapy and a 15-Gy boost administered as a part of brachytherapy. The management protocol was irrelevant from the standpoint of the study objective. The treatment plan was evaluated using a proprietary therapeutic protocol based on QUANTEC's suggestions.²⁵

Alignment control

Prior to each treatment session, the alignment was verified by means of kilovolt imaging including two perpendicular X-ray scans (2D-2D kV) or a CBCT (3D) scan.¹⁰ All sessions involving CBCT scans were taken into account in the analysis of study results. A total of 488 image sets were analyzed for 30 patients. For the CBCT-based alignment method, images were superimposed off-line by 3 electroradiology technicians and one physicist. For the method involving the use of gold fiducial marker as well as the method for determination of PG against the pubic symphysis, the analyses were performed by the medical physicist alone. In the CBCT-based method, images were superimposed using prostate gland outlines. In the

marker-based method, images were superimposed using markers visible in the treatment planning CT scans as well as the CBCT scans. For pubic symphysis-relative alignment images were superimposed using pubic symphysis outlines visible in the treatment planning CT scans as well as the CBCT scans. For each method, increments were determined by which the therapeutic bed should be moved in the anteroposterior (Vrt), craniocaudal (Lng), and transverse (Lat) directions so as to obtain the best match between the superimposed objects from the alignment control and treatment planning scans. No rotation was taken into account when superimposing images. Automatic overlay showed that in a vast majority of cases, the rotation angle was lower than 1.5°. All processing was done using the Off-line Review app of the Eclipse v. 13.6 treatment planning system. In the first two methods, image acquisition was carried out manually. In the pubic symphysis-related alignment method, images were acquired automatically. Automatic acquisition was limited to the pubic symphysis area. Depending on the number of radiation fractions delivered to each patient, a total of 11 to 19 image pairs were analyzed for each method depending on the number of CBCT examinations performed.

Analysis of results

In this study, the prostate gland-based alignment of CBCT images was assumed as the reference method. Another assumption was that the systematic error of the CBCT scan overlay was negligible compared to the casual error. The casual error for this method was determined from the CBCT results obtained for 5 patients subjected to 5 irradiation sessions as analyzed by 4 different observers.

To determine the uncertainty of the prostate gland-based alignment of CBCT images, standard deviations were calculated for the differences between the positions of planned and actual isocenters as determined by 4 different observers (3 technicians and 1 medical physicist) for each patient, each irradiation session, and each of the separate Vrt, Lng, and Lat directions. The description provided hereinafter shall pertain to a single direction. Mathematical processing is the same for all directions. The description pertains to a single patient and the z-axis

Taking into account the results obtained by n=4 observers for the mth session in the kth patient, the average difference is:

$$\bar{z}_{k,m} = \frac{\sum_{n=1}^4 z_{k,m,n}}{4} \quad \text{Eq. 1}$$

$z_{k,m,n}$ is the result obtained for the kth patient in the mth session by the nth observer.

The uncertainty of determination of the matching error for this session is:

$$stdev_{z,k,m} = \sqrt{\frac{\sum_{n=1}^4 (z_{k,m,n} - \bar{z}_{k,m})^2}{4-1}} \quad \text{Eq. 2}$$

The number of sessions analyzed for each patient was N = 5. Thus, standard deviation averaged for all sessions for the kth patient along the z axis was:

$$\overline{stdev}_{z,k} = \frac{\sum_{m=1}^5 stdev_{z,k,m}}{5} \quad \text{Eq. 3}$$

After averaging the results for 5 patients, one obtains the value of method uncertainty for the z axis:

$$\overline{stdev}_z = \frac{\sum_{k=1}^5 \overline{stdev}_{z,k}}{5} \quad \text{Eq. 4}$$

Errors for the other two directions were determined in a similar manner.

CTV-PTV margins

In order to determine the CTV-PTV margins, cumulative histograms were constructed for the moduli of differences between the locations of planned and actual isocenters as determined for the single marker/CBCT and pubic symphysis/CBCT methods. It was assumed that the value of the margin to be added to the CTV is represented by the root of the sum of the squares for the doubled value of method uncertainty for the CBCT image-based alignment method and the differences in the value of the uncertainty of the method to the CBCT images and the value of the difference between the locations of planned and actual isocenters as determined using the method of interest and the CBCT-based alignment method for which the total number of differences accounted for 95% of all differences, as well as a third component. The fact that the uncertainty of CBCT image superimposition was determined off-line was taken into account. In clinical practice, however, images are superimposed online and under the pressure of time which increases the uncertainty of image superimposition. Therefore, a random assumption was made that the necessity for quick image acquisition leads to casual error which can be described by uniform distribution over the range of ±2 mm. The variance of the uniform distribution is $4^2/12 = 1.15$ mm. This methodology was adopted because the analysis of results obtained for individual patients revealed a relatively large number of outliers along with the fact that in many cases, the differences did not follow the Gaussian distribution pattern. Values were validated as outliers using the Student's t-test with a confidence level of 95%. The normality of dose distributions was analyzed using the Shapiro-Wilk's test for the confidence level of 95%. Since distributions were found not to follow the normal distribution pattern, the usual methodology for the determination of margins as proposed by van Herk²⁹ could not be applied.

In this study, the margin along the z-axis, expressed in centimeters, was calculated from the following formula:

$$Mar_z = \sqrt{(2 \cdot stdev_z)^2 + (w_{z,95\%})^2} + 0,115^2 \quad \text{Eq. 5}$$

Results

In one of the examined patients, large differences between the planned and actual isocenters were observed due to the patient's anatomical traits (obesity). Offset values of > 1 cm were observed for the vertical and longitudinal directions; with regard to the lateral direction, however, changes in isocenter location were small and similar to those observed in the entire study group. The large offsets could have resulted from difficulties in aligning laser centrators with the patient's body markings.²³ Lilie L. Lin et al. found that obesity may affect the magnitude of interfractional offsets, systematic errors, and CTV-PTV margins to be used.²⁴ In view of the above, the patient was excluded from the procedure for setting the CTV-PTV margins using the selected methods. Individual management procedures should be followed in this case.

The uncertainty of the PG positioning method based on the acquisition of CBCT and CT images as determined from Formula 4 was 0.115 cm, 0.14 cm, and 0.095 cm for the Vrt, Lng and Lat directions, respectively.

The obtained uncertainties were used to determine the CTV-PTV margins to be used with the CBCT-based method. The obtained values were doubled and additional 2-mm margins were added for each of the Vrt and Lng directions. Due to the expected lower uncertainty along the Lat direction, the additional added margin was 1 mm wide. The additional margins of 1 mm and 2 mm were determined arbitrarily to account for the fact that the uncertainty of the method was determined by means of off-line superimposition of images. In real-world conditions, images are superimposed online which increases the uncertainty of superimposition. The respective margins for the Vrt, Lng, and Lat directions were 0.43 cm, 0.48 cm, 0.29 cm.

In the case of prostate-to-marker differences, the largest number of distributions that required the normality hypothesis being rejected was obtained for the vertical direction in 5 patients (16.7%). Also for prostate-to symphysis differences, the largest number of distributions that required the normality hypothesis being rejected was obtained for the vertical direction. Such results were obtained in 14 (46.7%) patients. The results of the Shapiro-Wilk test are presented in **Table 1**.

Figures 1 and **2** present frequency histograms for the calculated displacements: PG – symphysis, PG – marker for each individual direction (Vrt, Lng, Lat). Outlier values have been rejected from histograms. For the pubic symphysis-based alignment method, the outliers were identified in 65 out of 487 fractions (13.35%) for the vertical direction, 21 out of 487 fractions (4.31%) for the longitudinal direction, and 4 out of 487 fractions (0.82%) for the lateral direction. For the marker-based alignment method, the total numbers of outliers were 14 (2.87%), 22 (4.52%), and 4 (0.82%) for Vrt, Lng, and Lat directions, respectively.

For both analyzed pairs of methods for PG positioning, the mean displacements in all directions were not significantly different from zero (Student's t-test, 95% confidence level).

Figures 3 and **4** present cumulative histograms of the moduli of measurements for both pairs of methods being compared.

Slightly better conformity was obtained for vertical and longitudinal directions in the pubic symphysis-based alignment method. For the longitudinal direction, a 95% conformity level was achieved at 0.5 cm for the Lng direction and 0.45 cm for the Vrt direction. For the Lat direction, the pubic symphysis-based alignment method was characterized by 95% conformity achieved at 0.23 cm, as compared to 0.2 cm for the marker-based alignment method.

Table 2 lists the CTV-PTV margin values as calculated from **Equation 5**.

Table 1. Shapiro-Wilk's test for the normality of distributions of differences at the significance level of $\alpha = 0.05$.

	marker – prostate			prostate – symphysis		
	Vrt	Lng	Lat	Vrt	Lng	Lat
$\sum$ normal distributions	25 = 83.3%	26 = 86.7%	28 = 93.3%	16 = 53.3%	17 = 56.7%	24 = 80%
$\sum$ other distributions	5 = 16.7%	4 = 13.3%	2 = 6.7%	14 = 46.7%	13 = 43.3%	6 = 20%

Table 2. The obtained values of CTV-PTV margins.

method	direction		
	vertical [cm]	long [cm]	lateral [cm]
pubic symphysis	0.65	0.76	0.46
marker	0.7	0.88	0.44

Figure 1. Frequency histograms of the PG–symphysis displacements as calculated separately for each direction (Vrt, Lng, Lat).

Figure 2. Frequency histograms of the calculated PG–marker displacements as calculated separately for each direction (Vrt, Lng, Lat).

Figure 3. Cumulative histogram of the moduli of displacements for the PG–pubic symphysis method.

Figure 4 . Cumulative histogram of the moduli of displacements for the PG–marker method.

Discussion

The size of CTV-PTV margins being used has a huge impact on the protection of critical organs in the vicinity of the irradiated area. The smaller the margins, the smaller the doses absorbed by critical organs. At the same time, small margins are associated with a greater risk of underexposure within the target volume. Therefore, the determination of appropriate margins for each method used to position the PG in a particular radiation therapy center is important for the safety of the treatment.

The size of the margin is influenced by two factors, namely the accuracy of positioning and the mobility of the target area, usually determined against bone structures. For the prostate, the latter component plays an important role and should not be disregarded. Therefore, at many facilities, PG position is frequently determined on-line prior to each radiotherapy session. Generally, 3 or 4 fiducial markers made of gold are implanted prior to treatment to be clearly visible in the verification images for easier alignment of scans acquired as part of treatment planning as well as directly before the treatment session. At our unit, only one such marker is usually implanted. In patients with prostate cancer, on-line verification is performed daily during each treatment session by the alternate acquisition of two portal X-rays or a CBCT scan. In this study, we assessed the single marker-based alignment method and, in addition, the pubic symphysis-based alignment method using CBCT-based alignment method as the reference. In the latter case, we were guided by the results obtained by Piziorska who pointed out the method making use of pubic symphysis as the reference point for PG positioning as a good alternative to the CBCT-based alignment method.²⁸

The study revealed a very low uncertainty of the method involving the superimposition of CBCT scans and treatment planning CT scans. The uncertainty values were 0.115 cm, 0.14 cm, and 0.095 cm for the Vrt, Lng, and Lat directions, respectively. The results are surprisingly good and thus indirectly contradict the notion of poor quality of CBCT images and the associated difficulties in image superimposition. However, one should keep in mind that the uncertainty of this method was determined on the basis of off-line measurements with no time restrictions being enforced on the acquiring person. In real life, radiation technologists delivering treatment sessions are under the pressure of time which requires them to perform their job quickly. Increasing the superimposition times might result in the position of the prostate gland being changed which would thus increase the error of overlay. The lower accuracy of on-line superimposition is indirectly confirmed by the high number of outliers obtained for the two compared pairs of methods. Ultimately, the authors of this study determined that the proper CTV-PTV margins to be used when PG position is determined using CBCT scans are 0.43 cm, 0.48 cm, and 0.29 cm for the

Vrt, Lng, and Lat directions, respectively. Much higher values were mentioned by Yartsev et al., who stated margins should be in the range of 0.5-0.8 cm for each direction.⁷

The analysis of cumulative histograms of the moduli of prostate gland displacements as determined using the CBCT-based and the single-marker-based methods revealed these displacements were greater than 0.2 cm, 0.67 cm, and 0.52 cm for the Lat, Lng, and Vrt directions, respectively in 5% of treatment sessions. A satisfactory result was obtained for the lateral direction alone. With regard to the two remaining directions, the magnitude of discrepancy between both methods translates to the margins to be used when PG position is determined with the use of a single fiducial marker being large and amounting to 0.88 cm and 0.7 cm for the Lng and Vrt directions, respectively. Why do the results of PG positioning obtained using the marker-based method differ so much from the results of the CBCT image superimposition? Careful analysis of the placement of the fiducial marker within the prostate gland showed that in many patients, the marker was located on the edge of the prostate gland. Even small rotations of the prostate gland could have a significant impact on the obtained results.

One patient within the study population posed a significant problem in the attempts to recreate appropriate PG position due to their obesity. The results obtained for this patient were at least twice as large as the results obtained for the remaining study patients. In clinical practice, this would mean that they should be treated as "difficult", requiring more attention at every stage of the management process compared to all the other patients.²³

Conclusions

The results show that for all three methods for the verification of PG position, the smallest values were obtained for the lateral direction regardless of the method used for margin determination. The CBCT prostate imaging-based alignment method facilitates the use of the lowest CTV-PTV margins. The largest margin values were obtained for the method based on the position of a single gold marker. In the opinion of the authors, this result requires additional confirmation since many patients had their markers implanted in close proximity of the PG.

Acknowledgments

Authors would like to thank for help in creating the article to Norbert Nowicki (Medical Physics Department, University Hospital, Zielona Góra, Poland) and Justyna Żurawska-Kaczorowska (Radiotherapy Department, University Hospital, Zielona Góra, Poland).

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