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Neurovascular Bundle Infiltration Can Explain Local Relapses Using Conformal Radiotherapy of Prostate Cancer

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Abstract. *Aim: To quantify the impact of decreased margins for two treatment techniques, three-dimensional conformal radiotherapy (3D-CRT) and volumetric-modulated arc therapy (VMAT), on local control in curative treatment of prostate cancer. Materials and Methods: The planning target volume (PTV) margins were decreased in steps of 1 mm from 10 to 1 mm. Treatment plans using 3D-CRT and VMAT technique were produced for all margin sizes and the dose to the neuro vascular bundles (NVB), that was not included in the PTV, was investigated. Results: Due to the more conformal dose delivery using VMAT, the dose to the NVB decreased more rapidly by VMAT compared to the 3D-CRT plans. The dose difference was significant for margins from 1-7 mm. Conclusion: One should be very cautious before clinical routines are changed, bearing in mind whether the change means more conformal treatment technique, smaller margins or target segmentation in different imaging modalities.*

Prostate cancer (PC) is the most common cancer among men in Sweden, EU and North America. In Sweden, 9500 men develop PC each year and approximately 20% of all Swedish men will be diagnosed with PC during their lifetime. Each year, 2500 men die from PC in Sweden (which is 5% of all mortality). Many patients experience side-effects of their PC treatment such as rectal bleeding, incontinence and impotence. In addition to great costs for the society, these side-effects cause impaired quality of life for a long period of time.

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With technical advances in radiotherapy, such as three-dimensional conformal radiotherapy (3D-CRT) (1), intensity-modulated radiotherapy (IMRT) (2) and volumetric arc therapy (VMAT) (3), the conformity of the dose distribution has been improved (4). Despite this, in radiotherapy for PC, the proximity of the prostate and the organs at risk (OAR) are limiting factors (5).

The alteration in position and shape of the prostate and the OAR implies uncertainties in set-up and delivery of radiotherapy (6-8), which could lead to treatment fields partly or completely missing the target (9). In the International Commission on Radiation Units and Measurements (ICRU) report 50 an additional margin is applied to the delineated clinical target volume (CTV) to account for geometrical uncertainties, the planning target volume (PTV) (10).

The PTV margin has been reduced from typically 15-20 mm to 3-7 mm with the use of fiducial markers (11) and image-guided radiotherapy (IGRT) (12), where daily pre-treatment imaging was used to take into account the inter-fractional variation of the geometrical position of the prostate (13).

According to studies from Heemsbergen *et al.* (14) and Witte *et al.* (15), local control was reduced using IMRT compared to 3D-CRT box technique in patients with high-risk tumours. It has also been shown by Chao *et al.* that the microscopic spread in the neuro vascular bundles (NVBs) is dependent on the differentiation of the tumour (16).

In this comparative treatment planning study, we studied the difference in tumour control probability (TCP) in the NVBs for different PTV margins (1-10 mm in steps of 1 mm) using the 3D-CRT box technique and VMAT in order to explain the clinical observation in the above-mentioned studies.

Materials and Methods

Patients. Fourteen consecutive patients with biopsy-proven localized adenocarcinoma T1-T3NX/0MX/0 indicated for curative radiotherapy of localized PC were included in the study. The prostate CTV was 21 ml to 69 ml (mean=44 ml).

Table I. *The parameters used for the tumour control probability calculations for the clinical target volumes (CTV) and the neurovascular bundles (NVB). Four different α/β ratios were used.*

Stage/target	D_{50Gy}	Gamma	α/β Ratios (Gy)	Reference
C/CTV	63.30	5.00	1.5, 3.0, 6.0, 10.0	(17-23)
C/NVB	63.30	5.00	1.5, 3.0, 6.0, 10.0	(17-23)

Table II. *The parameters used for the normal tissue control probability calculations.*

Stage/organ	D_{50Gy}	Parameter m	α/β Ratio (Gy)	Parameter n	Reference
Grade>2/rectum	81.80	0.22	3.00	0.2900	(24)
Grade>3/bladder	62.00	0.11	6.00	0.13	(25)

Patient immobilization and positioning. For treatment planning purposes, all patients underwent computed tomographic (CT) scanning using 2.5 mm slice thickness. The patients were placed on their back on the table, and a knee and foot fixation was used.

Target volumes and OAR. The prostate gland was contoured and defined as the CTV, using magnetic resonance imaging (MRI) as support for target segmentation. The seminal vesicles were excluded from the CTV. The CTV to PTV margin was 1-10 mm in all directions, increased in steps of 1 mm for a total 10 PTVs for each patient (Figure 1). The NVBs were segmented separately and not included in the CTV, thus the NVBs did not affect the PTV. The NVB-CTV was defined as a circle of 7 mm (Figure 1) in order to cover 90% of microscopic spread in tumours with Gleason score 7 (16). The rectum, the bladder and the femoral heads were segmented as OAR. The length of the rectum was 3 cm above and below the CTV in the longitudinal direction and was defined as the whole content inside the outer wall. The bladder was segmented as the whole content inside the outer wall.

Treatment planning. For each patient in the study, two treatment plans for each PTV were made using 3D-CRT and VMAT respectively, which gave a total of 20 treatment plans per patient. The treatment plans were made in RayStation 5 (RaySearch laboratories, Stockholm, Sweden) using an in-house developed ironPython script, which is a built-in functionality in the treatment planning system. The treatment plans were made for an Elekta Synergy instrument (Elekta, Stockholm, Sweden) with an Agility multi-leaf collimator. The 3D-CRT treatment plan used four equally spaced beams (0. 90. 180 and 270 degrees) using 15 MV x-ray beams and the VMAT treatment plan one full arc (182-178 degrees) using 6 MV x-ray beams. All plans were calculated with a voxel size of 1×1×2.5 mm^3. The prescribed dose was 78 Gy in 39 fractions.

Evaluation criteria. The dose coverage of the PTV was to meet the criteria that 98% of the volume should receive at least 95% ($D_{98\%}$>95%) and 2% of the volume at most 107% ($D_{107\%}$<2%) of the prescribed dose (10). Due to different PTV margins, there were no dose evaluation criteria for the OAR. Depending on the size of the PTV, two levels of average dose to the rectum and the bladder were used as optimization criteria to reach a dose level in the OAR as low as possible with retained dose conformity to the PTV.

TCP was calculated for the prostate-CTV and the NVB-CTV, and normal tissue control probability (NTCP) was calculated for the rectum and the bladder. TCP and NTCP parameters are presented in Tables I and II, respectively. For TCP and NTCP calculations, the RayBiology module in RayStation was used.

Statistics. A paired, double sided t-test was used for both TCP and NTCP comparisons (Matlab 2016b, MathWorks Inc., Natick, MA, USA). A significance level of 5% was used. Only one *p*-value is mentioned for the cases where significance was shown in the results, due to the great number of *p*-values in this work. Instead, confidence intervals are used to show if the difference in TCP and NTCP was significant or not for each PTV margin. The difference was considered significant if the confidence interval did not contain zero.

Results

In Figure 2, the TCP values for 3D-CRT and VMAT are plotted for the left and right NVB and for the prostate.

The TCP values for the left and right NVB were calculated with four different α/β-values: 1.5, 3.0. 6.0 and 10 Gy (see Figure 2). The TCP values for both NVBs were significantly higher when the 3D-CRT technique was used for margins of 1-7 mm ($p<0.05$). The parameters used for the TCP model are shown in Table I.

In Figure 3, the NTCP values and their confidence intervals for the rectum and bladder are shown. The parameters used for the NTCP model are shown in Table II. There was a significant difference between the two treatment techniques for all margins used, both for the rectum and the bladder, where the probability for normal tissue complications were significantly lower when VMAT was used.

All treatment plans fulfilled the dose coverage criteria D98% >95% for the corresponding PTV. The mean TCP values for the prostate are shown in Figure 2.

There were no differences in TCP values for the prostate-CTV, regardless of PTV margin and α/β-value used (see Figure 2).

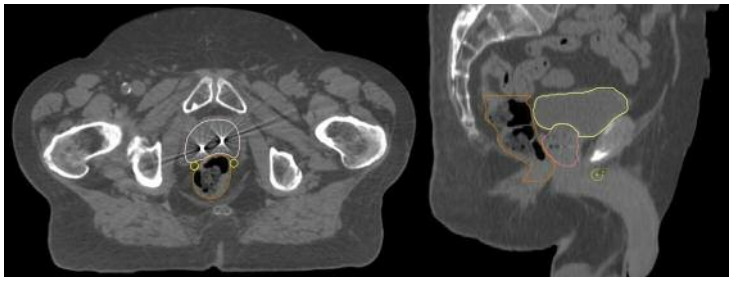

Figure 1. *Transversal and sagittal view of one representative patient. The rectum (brown), bladder (pale yellow), prostate-clinical target volume (CTV) (pink) and neurovascular bundle-CTV (yellow) are delineated.*

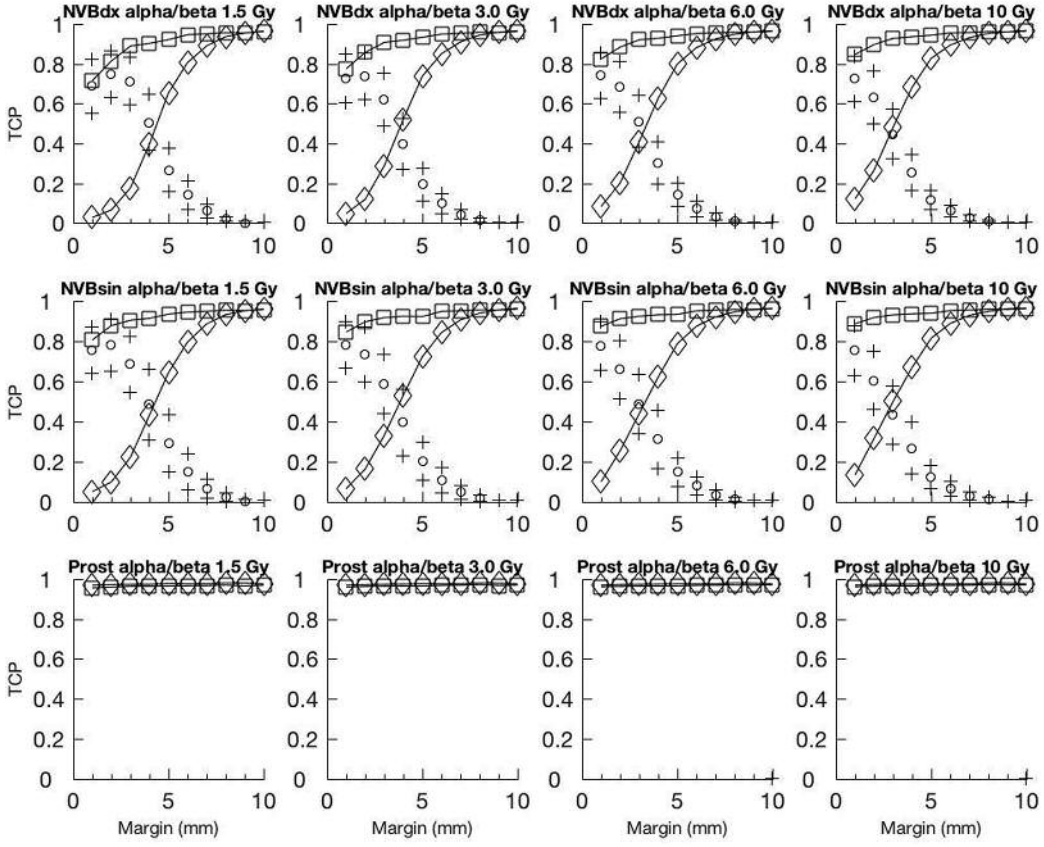

Figure 2. *Mean tumour control probability values by margin for all α/β-values by three-dimensional conformal radiotherapy (squares) and volumetric-modulated arc therapy (diamonds). The mean difference is shown as circles with its confidence interval (+).*

Discussion

There are at least two studies describing an increase in clinical local failure during radiotherapy of prostate cancer when the treatment techniques have become more conformal (14, 15). It has also been shown that the microscopic spread of tumour cells in the NVB is dependent on the differentiation of the tumour (16).

In this study, we investigated the impact on the TCP in the NVBs during radiotherapy of PC for different treatment techniques and margins. We showed that there was a significant difference in TCP for NVB-CTV using 3D-CRT

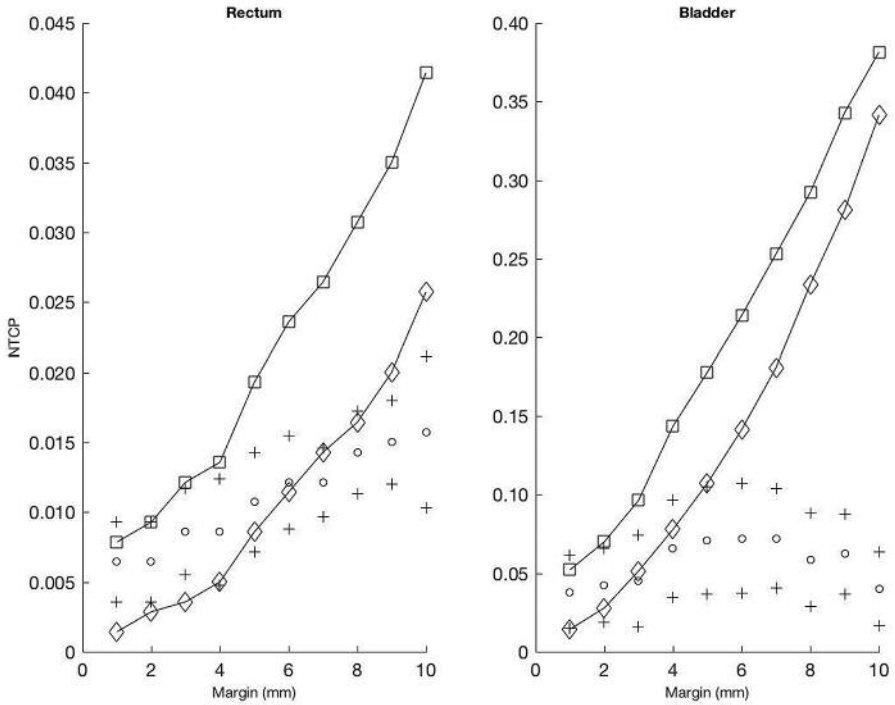

Figure 3. *Mean normal tissue control probability values for the rectum (left) and the bladder (right). Three-dimensional conformal radiotherapy is represented by squares and volumetric arc therapy by diamonds. The mean difference is shown as circles with its confidence interval (+).*

and VMAT for PTV margins up to 7 mm ($p<0.05$), where the TCP was higher when using 3D-CRT. For larger margins, the NVBs were included in the PTV and the TCP was similar for both treatment techniques. But the NTCP for the rectum and the bladder was significantly lower for VMAT, irrespective of margin, due to the more conformal dose distribution around the PTV.

This study confirms that in regard to the TCP in the NVB, more conformal techniques influence local control. The decreased local control is due to a more conformal dose distribution and the reduction of the PTV margins, which reduces side-effects. The margins can be safely reduced due to on-line verification of the prostate position (IGRT and fiducials). Therefore, this study shows the importance of better outlining of CTV in PC, taking into account information concerning microscopic spread in the NVBs and information of capsular infiltration for other investigations such as MRI. The disadvantage of a larger CTV is an increased dose to the rectum. By separating the rectum from the prostate using rectum spacers (26-31), the dose to the rectum will be lowered. This will be even more important when using small margins and very conformal techniques such as VMAT and proton therapy.

Even the modality in which the CTV is outlined affects the risk of small PTV margins. It has been shown by Gunnlaugsson and co-workers that the CTV is 23% larger when it is defined on computed tomography compared to defining it on MRI (32). They also showed that during extreme hypo-fractionated radiotherapy, the prostate increases in volume during the treatment by up to 15%. In this case, the risk of local relapse is larger when outlining the CTV on MRI if the same PTV margin is used for both computed tomography and MRI. Therefore, it is of great importance to understand the meaning of the PTV margin which has to be adapted to the modality used.

Since this is a treatment planning study, we only studied a static scenario, which explains the high TCP values for prostate-CTV regardless of the margin size since prostate-CTV is always inside the PTV. In this case, the TCP values are used as a measure of acceptable dose coverage of the CTV. For a dynamic case, the TCP values would decrease with decreasing PTV margin. In addition, the same parameters in the TCP model were used for both prostate and NVBs. However, in this case, the TCP value was used for relative comparisons and absolute values are of less importance.

There are clinical observations in which there were fewer local relapses after radiotherapy of PC when the treatment technique was less conformal (14, 15). This study shows that the dose coverage of the NVBs decreases when narrower

PTV margins are used in combination with changing treatment technique from 3D-CRT to VMAT. Therefore, one should be very cautious before clinical routines are changed, as to whether the change means more conformal treatment technique, smaller margins or target segmentation in different imaging modalities.

Conflicts of Interest

The Authors have no conflicts of interest to report. The Authors alone are responsible for the content and writing of the article.

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References

1 Fiveash JB, Hanks G, Roach M, Wang S, Vigneault E, McLaughlin PW and Sandler HM: 3D Conformal radiation therapy (3DCRT) for high-grade prostate cancer: a multi-institutional review. Int J Radiat Oncol Biol Phys *47(2)*: 335-342, 2000.

2 Zelefsky MJ, Fuks Z, Happersett L, Lee HJ, Ling CC, Burman CM, Hunt M, Wolfe T, Venkatraman ES, Jackson A, Skwarchuk M and Leibel SA: Clinical experience with intensity modulated radiation therapy (IMRT) in prostate cancer. Radiother Oncol *55(3)*: 241-249, 2000.

3 Wolff D, Stieler F, Welzel G, Lorenz F, Abo-Madyan Y and Mai S, Herskind C, Polednik M, Steil V, Wenz F and Lohr F: Volumetric-modulated arc therapy (VMAT) *vs*. serial tomotherapy, step-and-shoot IMRT and 3D-conformal RT for treatment of prostate cancer. Radiother Oncol *93(2)*: 226-233, 2009.

4 Palma D, Vollans E, James K, Nakano S, Moiseenko V, Shaffer R, McKenzie M, Morris J and Otto K: Volumetric-modulated arc therapy for delivery of prostate radiotherapy: comparison with intensity-modulated radiotherapy and three-dimensional conformal radiotherapy. Int J Radiat Oncol Biol Phys *72(4)*: 996-1001, 2008.

5 Haverkort MAD, van de Kamer JB, Pieters BR, van Tienhoven G, Assendelft E, Lensing AL, van Herk M, de Reijke TM, Stoker J and Koning CCE: Position verification for the prostate: effect on rectal wall dose. Int J Radiat Oncol Biol Phys *80(2)*: 462-468, 2011.

6 van Herk M, Bruce A, Kroes AP, Shouman T, Touw A and Lebesque JV: Quantification of organ motion during conformal radiotherapy of the prostate by three-dimensional image registration. Int J Radiat Oncol Biol Phys *33(5)*: 1311-1320, 1995.

7 Deurloo KEI, Steenbakkers RJHM, Zijp LJ, de Bois J, Nowak PJCM, Rasch CRN and van Herk M: Quantification of shape variation of prostate and seminal vesicles during external beam radiotherapy. Int J Radiat Oncol Biol Phys *61(1)*: 228-238, 2005.

8 Li HS, Chetty IJ, Enke C, Foster RD, Willoughby TR, Kupellian P and Solberg TD: Dosimetric consequences of intrafraction prostate motion. Int J Radiat Oncol Biol Phys *71(3)*: 801-812, 2008.

9 Azcona JD, Xing L, Chen X, Bush K and Li R: Assessing the dosimetric impact of real-time prostate motion during volumetric-modulated arc therapy. Radiat Oncol Biol *88(5)*: 1167-1174, 2014.

10 Prescribing R and Therapy RPB: ICRU Report no 50 - Prescribing, Recording and Reporting Photon Beam Therapy. International Commission on Radiation Units and Measurements, Bethesda, MD, 1993.

11 Soete G, De Cock M, Verellen D, Michielsen D, Keuppens F and Storme G: X-ray-assisted positioning of patients treated by conformal arc radiotherapy for prostate cancer: comparison of setup accuracy using implanted markers *versus* bony structures. Int J Radiat Oncol Biol Phys *67(3)*: 823-827, 2007.

12 Eade TN, Guo L, Forde E, Vaux K, Vass J, Hunt P and Kneebone A: Image-guided dose-escalated intensity-modulated radiation therapy for prostate cancer: treating to doses beyond 78 Gy. BJU Int *109(11)*: 1655-1660, 2012.

13 Wu Q, Ivaldi G, Liang J, Lockman D, Yan D and Martinez A: Geometric and dosimetric evaluations of an online image-guidance strategy for 3D-CRT of prostate cancer. Int J Radiat Oncol Biol Phys *64(5)*: 1596-1609, 2006.

14 Heemsbergen WD, Al-Mamgani A and Slot A, Dielwart MFH and Lebesque JV: Long-term results of the Dutch randomized prostate cancer trial: impact of dose-escalation on local, biochemical, clinical failure, and survival. Radiother Oncol *110(1)*: 104-109, 2014.

15 Witte MG, Heemsbergen WD, Bohoslavsky R, Pos FJ, Al-Mamgani A and Lebesque JV and van Herk M: Relating dose outside the prostate with freedom from failure in the Dutch trial 68 Gy *vs*. 78 Gy. Int J Radiat Oncol Biol Phys *77(1)*: 131-138, 2010.

16 Chao KK, Goldstein NS, Yan D, Vargas CE, Ghilezan MI, Korman HJ, Kernen KM, Hollander JB, Gonzalez J, Martinez A, Vicini F and Kestin LL: Clinicopathologic analysis of extracapsular extension in prostate cancer: Should the clinical target volume be expanded posterolaterally to account for microscopic extension? Int J Radiat Oncol Biol Phys *65(4)*: 999-1007, 2006.

17 Brenner DJ and Hall EJ: Fractionation and protraction for radiotherapy of prostate carcinoma. Int J Radiat Oncol Biol Phys *43(5)*: 1095-1101, 1999.

18 Wang JZ, Guerrero M and Li XA: How low is the α/β ratio for prostate cancer? Int J Radiat Oncol Biol Phys *55(1)*: 194-203, 2003.

19 Kal H and Vangellekom M: How low is the α/β ratio for prostate cancer? Int J Radiat Oncol Biol Phys *57(4)*: 1116-1121, 2003.

20 Carlson DJ, Stewart RD, Li XA, Jennings K, Wang JZ and Guerrero M: Comparison of *in vitro* and *in vivo* α/β ratios for prostate cancer. Phys Med Biol *49(19)*: 4477-4491, 2004.

21 Nahum AE, Movsas B, Horwitz EM, Corinne CS and Chapman JD: Incorporating clinical measurements of hypoxia into tumor local control modeling of prostate cancer: Implications for the α/β ratio. Int J Radiat Oncol Biol Phys *57(2)*: 391-401, 2003.

22 Yeoh EE, Botten RJ, Butters J, Di Matteo AC, Holloway RH and Fowler J: Hypofractionated *versus* conventionally fractionated radiotherapy for prostate carcinoma: Final results of phase III randomized trial. Int J Radiat Oncol Biol Phys *81(5)*: 1-8, 2010.

23 Bentzen SM and Ritter MA: The alpha/beta ratio for prostate cancer: what is it, really? Radiother Oncol *76(1)*: 1-3, 2005.

24 Rancati T, Fiorino C, Gagliardi G, Cattaneo GM, Sanguineti G, Borca VC, Cozzarini C, Fellin G, Foppiano F, Girelli G,

Menegotti L, Piazzolla A, Vavassori V and Valdagni R: Fitting late rectal bleeding data using different NTCP models: Results from an Italian multi-centric study (AIROPROS0101). Radiother Oncol *73(1)*: 21-32, 2004.

25 Dale E, Hellebust TP, Skjønsberg A, Høgberg T and Olsen DR: Modeling normal tissue complication probability from repetitive computed tomography scans during fractionated high-dose-rate brachytherapy and external beam radiotherapy of the uterine cervix. Int J Radiat Oncol Biol Phys *47(4)*: 963-971, 2000.

26 Nilsson K, Johansson AK, Montelius A, Turesson I, Heikkinen RO, Ljung G and Isacsson U: Decreasing the dose to the rectal wall by using a rectal retractor during radiotherapy of prostate cancer: a comparative treatment planning study. J Radiother *2014*: 1-7, 2014.

27 Isacsson U, Nilsson K, Asplund S, Morhed E, Montelius A and Turesson I: A method to separate the rectum from the prostate during proton beam radiotherapy of prostate cancer patients. Acta Oncol *49(4)*: 500-505, 2010.

28 Prada PJ, Fernández J, Martinez A, de la Rúa A, Gonzalez JM, Fernandez JM and Juan G: Transperineal injection of hyaluronic acid in anterior perirectal fat to decrease rectal toxicity from radiation delivered with intensity modulated brachytherapy or EBRT for prostate cancer patients. Int J Radiat Oncol Biol Phys *69(1)*: 95-102, 2007.

29 Pinkawa M, Corral NE, Caffaro M, Piroth MD, Holy R, Djukic V, Otto G, Schoth F and Eble MJ: Application of a spacer gel to optimize three-dimensional conformal and intensity modulated radiotherapy for prostate cancer. Radiother Oncol *100(3)*: 436-441, 2011.

30 Wachter S, Gerstner N, Dorner D, Goldner G, Colotto A, Wambersie A, Pötter R: The influence of a rectal balloon tube as internal immobilization device on variations of volumes and dose–volume histograms during treatment course of conformal radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys *52(1)*: 91-100, 2002.

31 Patel RR, Orton N, Tomé WA, Chappell R and Ritter MA: Rectal dose-sparing with a balloon catheter and ultrasound localization in conformal radiation therapy for prostate cancer. Radiother Oncol *67(3)*: 285-294, 2003.

32 Gunnlaugsson A, Kjellén E, Hagberg O, Thellenberg-Karlsson C and Widmark A and Nilsson P: Change in prostate volume during extreme hypo-fractionation analysed with MRI. Radiat Oncol *9(22)*: 1-6, 2014.

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