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Optimization of prostate cancer radiotherapy using of a spacer gel, volumetric modulated arc therapy and a single biological organ at risk objective

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► ***Original article***

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ABSTRACT

Background: The aim was to evaluate the benefit of technical advances for treatment planning: introduction of a hydrogel spacer, VMAT (volumetric modulated arc therapy) and a single biological organ at risk objective for the rectum and bladder. Initial standard was a step-and-shoot IMRT (intensity modulated radiotherapy) without a spacer and conventional organ at risk objectives. ***Materials and Methods***: Treatment plans were calculated using IMRT and VMAT techniques before and after spacer injection in 27 patients, respectively. Conventional organ at risk objectives have been used for the optimization of IMRT plans, only a single biological organ at risk objective for VMAT plans. VMAT vs. IMRT plans and plans before vs. after spacer injection were compared. ***Results:*** VMAT plans and independently the spacer demonstrated improved dose homogeneity, whereas VMAT additionally displayed improved dose conformity. The dose to the bladder and rectum could be significantly decreased applying the VMAT technique (mean rectum volumes of 14%/10%/5% in VMAT vs. 36%/24%/12% in IMRT within the 50Gy/60Gy/70Gy isodoses; $p<0.01$). NTCP for ≥grade 3 rectum toxicity could be accordingly decreased with the VMAT technique (3.6 vs. 0.9% for IMRT vs. VMAT; $p<0.01$) and the spacer gel (3.3 vs. 1.2% for plans without vs. with spacer gel; $p<0.01$) – only 0.3% with VMAT and spacer gel. ***Conclusion:*** In addition to the decreased rectal dose following spacer injection, VMAT with single biological organ at risk optimization resulted in further dose reduction to the organs at risk and improved dose homogeneity and conformity in comparison to the step-and-shoot IMRT technique with conventional objectives.

Keywords: *Prostate cancer, intensity-modulated radiotherapy, volumetric modulated arc therapy, treatment planning, spacer gel.*

INTRODUCTION

Recently developed technical advances allow a safer dose escalation in external beam radiotherapy for prostate cancer. Randomized dose escalation studies have demonstrated a considerable advantage for biochemical tumor control – however, with the disadvantage for higher rectal toxicity rates [1]. These studies have used conventional three-dimensional planning techniques. Currently, intensity-modulated radiotherapy (IMRT) is considered as a standard technique in many radiotherapy departments [2]. Apart from the frequently used step-and-shoot IMRT technique, dynamic rotational techniques are increasingly introduced in the treatment of

prostate cancer [3, 4]. The obvious advantage is a treatment from multiple angles in a short time, comfortable for the patient and reducing the probability of prostate displacement during a treatment fraction.

Biodegradable spacers, including hydrogel, hyaluronic acid, collagen or an implantable balloon, are increasingly used in the last years [5]. Spacers can be injected or inserted in a short procedure under transrectal ultrasound guidance via a transperineal approach. A distance of about 1.0-1.5cm is usually achieved between the prostate and rectum, excluding the rectal wall from the high isodoses [6]. A considerable dose reduction to the rectum following the application of a spacer between the prostate and anterior rectal wall has been shown in several studies [5, 7-9]. Several studies have shown well tolerated injection procedures and treatments [10, 11]. Apart from considerable reduction of rectal irradiation, the first prospective randomized trial recently demonstrated a reduction of rectal toxicity after hydrogel injection in men undergoing prostate image-guided intensity-modulated radiation therapy [7].

The aim of this study was to evaluate the impact of recent technical advances on the dose distribution and normal tissue complication probability (NTCP), based on the actual developments in a specific radiotherapy department. This study focuses specifically on innovative treatment planning with a single biological organ at risk objective for the rectum and bladder, respectively, as a simple efficient method in comparison to the conventionally used organ at risk objectives. A single biological organ at risk objective is based on the equivalent uniform dose (EUD) that represents the dose-volume histogram in only a single dose value – in contrast to several objectives for specific dose-volume levels that are used conventionally [12].

Initial plan optimization for IMRT with fixed organ at risk objectives was compared to the optimization with a single biological organ at risk objective that is currently used for VMAT plans in our department. All treatment plans were calculated with and without a hydrogel spacer to evaluate and compare the advantage to plan optimization/change of treatment technique alone (initial standard: IMRT with fixed organ at risk objectives and without spacer; current standard: VMAT with single biological organ at risk objective and spacer).

Prior studies in the literature have already compared IMRT and VMAT techniques with the same optimization criteria for both techniques [13-15]; this comparison has not been repeated in our study.

MATERIALS AND METHODS

Treatment planning

A polyethylene glycol spacer gel (10ml SpaceOAR™, Augmenix Inc., Waltham, MA) was injected under transrectal ultrasound guidance in 27 patients with localized stage T1-2cN0M0 prostate cancer (Gleason score ≤7; PSA<20ng/ml). It maintains space for approximately three months and is absorbed in approximately six months. The study was performed in accordance with the ethical guidelines laid out in the Declaration of Helsinki. All persons gave their informed consent prior to the inclusion in the study. Treatment planning computed tomography (CT) was performed before and 3-5 days after injection in supine position with a slice thickness of 5mm. Patients were asked to have a full bladder for the planning CT scans. They were asked to empty their bowels. In all scans prostate volume, planning target volume (PTV), bladder and rectum were delineated by identifying the external contours. The rectum enclosed the region from the anal canal to the rectosigmoid flexure. Clinical target volume (CTV) was defined as prostate with or without the base of seminal vesicles (corresponding to the proximal 2-4 seminal vesicle slices). The same individual (M.P.) performed all contouring to exclude inter-observer variations. For the PTV, 8mm lateral and anterior, 5mm superior and inferior and 4mm posterior margins were added.

Treatment plans were calculated using the IMRT (five step-and-shoot angles: 108°, 105°,

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45°, 315°, 255°) and VMAT (single full gantry rotation) techniques, respectively, resulting in 54 plans before and 54 plans after spacer injection (Philips Pinnacle^3 treatment planning system). Total dose was 78Gy (prescription dose) in 2Gy fractions in all cases. Dose distributions were optimized for 98% of the PTV volume receiving at least 95% of the prescribed dose while the maximum dose was kept below 107%.

Fixed rectum and bladder objectives have been used for the optimization of IMRT plans, with maximum rectum V_{50} = 50%, maximum rectum V_{70} = 20% (i.e. maximum 50% / 20% of the rectum volume within the 50Gy / 70Gy isodose level); maximum bladder V_{55} = 50%, maximum bladder V_{70} = 30% - based on RTOG (Radiation Therapy Oncology Group) recommendations [16]. The direct machine parameter optimization (DMPO) algorithm was applied for inverse planning with a 2cm^2 minimum segment area, 5 minimum segment monitor units and a maximum number of 70 segments.

EUD based planning was introduced for the optimization of VMAT plans. Only a single EUD value was used as rectum and bladder constraint, respectively. The EUD is defined as the biologically equivalent dose that, if given uniformly, will lead to the same effect in the tumor volume or the normal tissues as the actual nonuniform dose distribution [12]. The EUD objective was decreased consecutively (optimization repeated) as long as the dose to the PTV was not compromised. The dose to femoral heads was limited to a maximum of 50Gy to 2% of the femoral head in all treatment plans of this study without further optimization. Collimator position was set to 3°. The SmartArc algorithm was used for inverse planning with preset values of 300 sec maximum treatment time and limited leaf motion of 0.4 cm per degree.

Plan evaluation

Minimum dose, homogeneity and conformity for the PTV [17, 18] maximum doses to the rectum and bladder, as well as the respective dose-volume histograms were evaluated and compared.

$$\textit{Homogeneity index } HI = \frac{D_2 - D_{98}}{D_{50}}$$

D_2 / D_{98} / D_{50} – dose to 2% (maximum dose), to 98% (minimum dose) and 50% of PTV

$$\textit{Conformity Index } CI = \frac{PTV_{PIV}{}^2}{PTV * PIV}$$

PTV_{PIV} - PTV volume covered by 95% of the prescription dose

PIV – total volume covered by 95% of the prescription dose

Additionally, EUD and NTCP were determined. The form

$$EUD = \left(\frac{1}{N} \sum_i D_i^a \right)^{\frac{1}{a}}$$

was suggested for both tumors and normal tissues [12]: "N" is the number of voxels in the anatomic structure of interest, "D_i" is the dose in the i'th voxel, and "a" is the tumor or normal tissue-specific parameter that describes the dose -volume effect. In this analysis, a=-10 was taken for prostate cancer [12, 19], a=2 for the bladder and a=9 for the rectum [20, 21].

NTCP can be represented as a function of EUD. The equation is an exponential of a second-degree polynomial of the EUD (20). NTCP for rectum (severe proctitis, necrosis, fistula) and bladder (symptomatic bladder contracture and volume loss) [20, 21] toxicity was computed applying the Lyman-Kutcher-Burman model with Emami parameters (rectum: n=0.12, m=0.15, median toxicity dose=80Gy; bladder: n=0.5, m=0.11; median toxicity dose=80Gy). Additionally, parameters as published by Rancati *et al.* [22] for grade 2 or 3 rectal bleeding were applied.

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics 22.0 (IBM, New York), software. The Wilcoxon's matched-pairs test was applied to determine statistical differences between volumes, doses and NTCP for comparisons of IMRT vs. VMAT and pre spacer vs. post spacer plans. All p-values reported are two-sided, $p<0.05$ is considered significant.

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RESULTS

No statistical differences were found for the CTV, PTV and organ at risk volumes, as determined before and after spacer injections (table 1), though rectum and bladder volumes tended to be smaller in the post spacer CT. The dose delivered to the PTV is described with several values and indices in table 2. A significantly improved dose homogeneity and conformity in the PTV resulted in VMAT plans in comparison to IMRT plans. The EUD for the PTV was higher in VMAT plans, but minimum doses in the PTV were comparable (difference not significant). The application of a spacer resulted in improved homogeneity, but additionally a higher minimum dose in the PTV. Thus, the highest EUD, D_{min} and V_{76}, best homogeneity and conformity resulted in the VMAT plans following hydrogel injection.

The isodose distribution in IMRT and VMAT plans, well demonstrating the effect of the chosen techniques itself (five field IMRT with no objectives for lower dose levels and VMAT with maximum posterior dose drop-off) and the effect of the spacer on rectum protection is shown in figure 1 as an example. Mean dose-volume histograms for the bladder (figure 2) and rectum (figure 3) give an overview of all dose levels. Specific numbers with standard deviations are presented in table 3.

Table 1. Mean volumes before and after spacer gel injection (standard deviation).

	pre spacer (n=27)	**post spacer (n=27)**
planning target volume (cm^3)	131 (46)	136 (46)
prostate +/- base of seminal vesicles (cm^3)	56 (25)	55 (26)
rectum (cm^3)	96 (55)	88 (44)
bladder (cm^3)	230 (107)	217 (129)

Table 2. Comparison of mean dose values, homogeneity indices (HI) and conformity indices (CI) for the planning target volume (standard deviation). Statistically significant differences between VMAT and IMRT (first comparison) or pre spacer and post spacer (second comparison) in bold numbers (n.s.–not significant).

		VMAT (n=54)	**IMRT (n=54)**	**pre spacer (n=54)**	**post spacer (n=54)**	***VMAT +spacer (n=27)***
PTV	EUD / Gy	**77.7(0.3)**	**77.4(0.9)**	77.7(0.2)	77.6(0.7)	*77.7(0.2)*
		p=0.02		**n.s.**		
	D_{min} / Gy	75.1(0.8)	74.9(1.3)	74.7(1.2)	75.2(0.8)	*75.2(0.6)*
		n.s.		**n.s.**		
	V_{76} / %	**90.6(18.1)**	**81.7(25.0)**	**80.0(27.9)**	**92.3(11.8)**	*94.1(2.4)*
		p=0.01		**p=0.01**		
	HI	**0.05(0.01)**	**0.06(0.02)**	**0.06(0.02)**	**0.05(0.02)**	*0.05(0.01)*
		p=0.03		**p=0.02**		
	CI	**0.82(0.17)**	**0.73(0.07)**	0.76(0.17)	0.78(0.09)	*0.84(0.04)*
		p<0.01		**n.s.**		

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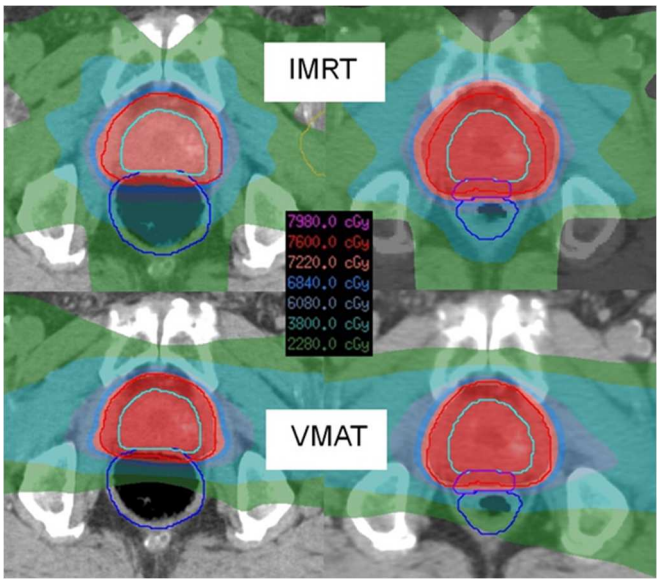


Figure 1. Example demonstrating isodose distribution applying IMRT (upper images) and VMAT (lower images) techniques without (left) and with (right) a hydrogel spacer in an axial planning computed tomography slice.

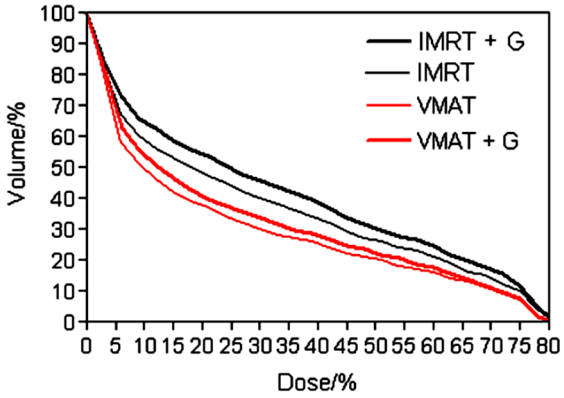


Figure 2. Mean bladder dose-volume histogram values for IMRT and VMAT plans without and with ("+ G") a hydrogel spacer.

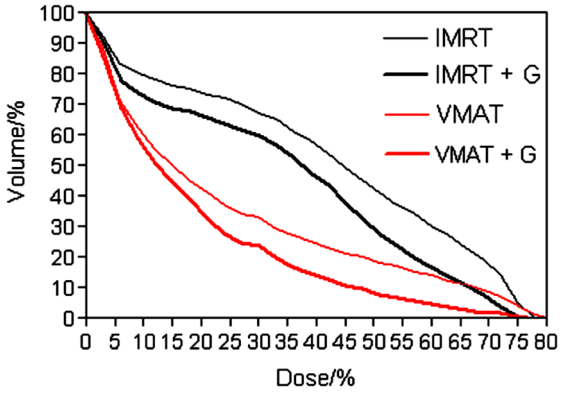


Figure 3. Mean rectum dose-volume histogram values for IMRT and VMAT plans without and with ("+ G") a hydrogel spacer.

Treatment technique and spacer injection play both an important independent role. The dose to the bladder and the rectum could be significantly decreased with the VMAT technique and biological plan optimization. Most probably as an effect of smaller bladder volumes, bladder doses were found to be higher after spacer injection. However, no significant spacer effect resulted for the bladder EUD and NTCP. NTCP for higher grade bladder toxicity was 0% in the majority of plans.

Considerably larger effects could be seen for the rectum dose. In spite of improved PTV dose coverage, EUD and NTCP for ≥grade 2 rectal bleeding and ≥grade 3 rectum toxicity could be significantly decreased ($p<0.01$), so that the best treatment plans again resulted using the VMAT technique with a single biological organ at risk objective following hydrogel injection. Mean NTCP was <1% and mean rectum V_{70}<2% combining both factors.

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Table 3. Comparison of mean dose values and normal tissue complication probability (NTCP) for the organs at risk (standard deviation). Statistically significant differences between VMAT and IMRT (first comparison) or pre spacer and post spacer (second comparison) in bold numbers (n.s.–not significant).

		VMAT (n=54)	IMRT (n=54)	pre spacer (n=54)	post spacer (n=54)	*VMAT +spacer (n=27)*
Rectum	EUD / Gy	**53.9(7.1)**	**58.9(6.7)**	**59.9(6.0)**	**52.9(6.9)**	*49.1(6.9)*
		p<0.01		**p<0.01**		
	D_{max} / Gy	**70.7(9.5)**	**73.7(3.5)**	**76.1(1.2)**	**68.2(8.6)**	*64.8(10.5)*
		p=0.03		**p<0.01**		
	V_{76} / %	**0.9(1.5)**	**1.6(1.9)**	**2.2(2.0)**	**0.4(0.6)**	*0.4(0.6)*
		p<0.01		**p<0.01**		
	V_{70} / %	**4.6(4.2)**	**10.7(8.5)**	**11.7(7.8)**	**3.6(3.8)**	*1.9(2.0)*
		p<0.01		**p<0.01**		
	V_{60} / %	**8.4(6.4)**	**20.4(12.4)**	**19.7(12.0)**	**9.1(8.2)**	*4.6(4.0)*
		p<0.01		**p<0.01**		
	V_{50} / %	**12.3(8.5)**	**30.7(16.3)**	**27.3(16.6)**	**15.7(12.8)**	*7.8(6.0)*
		p<0.01		**p<0.01**		
	NTCP / % (severe proctitis, necrosis, fistula)	**0.9(0.9)**	**3.6(2.5)**	**3.3(2.5)**	**1.2(1.6)**	*0.3(0.5)*
		p<0.01		**p<0.01**		
	NTCP / % (≥grade 2 rectal bleeding)	**1.9(1.7)**	**4.7(3.1)**	**4.9(2.8)**	**1.6(1.8)**	*0.6(1.0)*
		p<0.01		**p<0.01**		
Bladder	EUD / Gy	**35.1(9.3)**	**40.3(10.6)**	36.6(9.9)	38.8(10.6)	*35.7(9.3)*
		p<0.01		n.s.		
	D_{max} / Gy	**77.3(3.2)**	**78.0(1.9)**	77.3(3.5)	78.0(1.1)	*77.7(0.8)*
		p=0.04		n.s.		
	V_{76} / %	**12.0(6.1)**	**17.5(11.1)**	**13.6(8.8)**	**15.9(9.7)**	*12.3(6.3)*
		p<0.01		**p<0.01**		
	V_{70} / %	**22.0(11.3)**	**29.9(16.6)**	**24.5(12.7)**	**27.5(16.4)**	*22.4(11.8)*
		p<0.01		**p<0.01**		
	V_{60} / %	**32.8(16.7)**	**43.5(22.5)**	**36.2(18.1)**	**40.1(22.6)**	*34.0(17.9)*
		p<0.01		**p=0.04**		
	V_{50} / %	**42.3(21.7)**	**54.7(26.7)**	**46.1(22.2)**	**50.9(27.4)**	*43.8(23.1)*
		p<0.01		**p=0.02**		
	NTCP / % (symptomatic bladder contracture and volume loss)	**0.0(0.0)**	**0.1(0.3)**	0.0(0.2)	0.1(0.2)	*0.0(0.0)*
		p=0.03		n.s.		
right femoral head; D_{mean} / Gy Gy		**31.0(9.1)**	**25.0(7.9)**	28.5(9.7)	29.5(8.1)	*32.4(8.5)*
		p<0.01		n.s		
left femoral head; D_{mean} / Gy		**33.7(9.8)**	**26.5(8.9)**	30.7(8.7)	29.5(11.2)	*33.9(8.7)*
		p<0.01		n.s		

DISCUSSION

In this study we have evaluated the technical developments in our department. After the implementation of the IMRT technique, used as a five-field step-and-shoot technique, a hydrogel spacer injection was introduced. Using the RTOG treatment planning constraints [16], acceptable plans resulted even without a spacer. With the same constraints, the rectal volume in the high dose region, as for example V_{70}, was reduced by more than 50%. The available new methods allow rectal dose reductions far below the usually applied levels. The crucial difference is

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repeated optimization to reach the lowest possible dose to the organs at risk instead of the same fixed dose constraint for all patients.

Increasing the number of beam directions and beam segments, as established in IMRT techniques, above all improves dose conformity and decreases the dose to organs at risk [23]. Rotational techniques, as the VMAT technique, are available in linear accelerators since a few years. They enabled us to reduce the treatment time and the number of monitor units considerably. The number of beam directions increases considerably, simultaneously changing gantry speed, multileaf collimator position, and dose rate [4, 23]. An improved dose conformity and dose homogeneity in the PTV has been demonstrated in our study, as in other studies in the past [13, 24].

The application of fixed conventional dose constraints is not sufficient to reach the best possible result for the patient. The dose to the organs at risk needs to be as low as possible. Therefore, the inverse treatment planning optimization process must apply individually adapted constraints and/or needs to be repeated several times. As the EUD represents the dose to an organ by a single value, EUD based treatment planning allows us to use only a single objective for each organ at risk, based on known correlations of dose-volume histograms with consequential toxicity profiles [12, 19]. This planning method proved to be very effective in our clinical practice, particularly with a hydrogel spacer. The actual benefit of this method was evaluated in this study, using exactly the same patients for all treatment plans without and with a spacer. Prior studies have already shown a considerable rectal dose reduction applying the hydrogel spacer for prostate cancer IMRT, reducing mean V_{70} from 12-13% to 3-5% [7, 8]. The VMAT technique with a single biological organ at risk objective and a spacer allowed to reduce mean V_{70} to 1.9% and NTCP for severe rectal and bladder toxicity to <1%. The calculated NTCP for grade 2 or higher rectal bleeding was also <1%.

Techniques combining IMRT with static beam directions and VMAT optimization have been also evaluated in recently published studies to reduce the dose to the organs at risk and also to reduce the low dose spillage [4, 23]. Only small differences in comparison to VMAT optimization have been shown in prostate cancer patients, as an average rectum V_{70} of 14.9% with the VMAT technique and 12.9% with the hybrid technique in a study by Amaloo *et al.* [23] (prescription dose of 79.2Gy). Another study reported mean rectum V_{70} of 5.9% with IMRT and 5.6% with VMAT (prescription dose of 74Gy) [13]. These studies all used inverse treatment planning with several fixed dose-volume objectives for the rectum or bladder. NTCP or EUD has not been analysed.

Differences demonstrated in our study are considerably larger and thus clinically relevant, indicating that they have not been achieved by the treatment technique alone, but the application of the hydrogel and treatment plan optimization with a single biological organ at risk objective for the rectum and bladder, respectively.

CONCLUSION

This study demonstrates that a modern dose escalated prostate cancer treatment, applying a spacer and a VMAT technique, can be performed almost without any risk of serious late bladder and rectum toxicity. The reported very low organ at risk doses could not be reached in previously published studies, so that we can recommend this concept for other radiotherapy departments.

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***Conflicts of interest*:** *Declared none.*

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