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Quality of life > 5 years after prostate cancer radiation therapy with a radiopaque viscous hydrogel spacer

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► ***Original article***

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ABSTRACT

Background: Perirectal spacers are injected to decrease the dose to the rectum and prevent rectal toxicity in prostate cancer radiotherapy. Advantages of a radiopaque viscous hydrogel spacer are a good visibility in computed tomography and improved placement control. The aim of this study was to demonstrate unaffected long-term bowel quality of life (QoL) in comparison to baseline levels, independently from radiotherapy (RT) treatment technique. ***Materials and Methods:*** Patients responded to the EPIC (Expanded Prostate Cancer Index Composite) questionnaire before RT, at the last day of RT, 3 months, >12 months and >60 months after RT (n=27). A significant QoL change was defined as a statistically significant mean change >5 points in comparison to baseline. ***Results:*** The largest mean bowel domain changes were found at the end of RT (>10 points in the function and bother subdomains, respectively). Function subdomain changes remained without a significant difference in comparison to baseline at all later points in time (<3 points, respectively). In the bother subdomain, changes remained >5 points and statistically significant (8 and 6 points after >12 and >60 months, repsectively). In contrast to patients after pelvic node RT, the difference after >60 months was <5 points for patients after prostate only RT (12 vs. 4 points with vs. without pelvic node RT). ***Conclusion:*** The first QoL analysis after RT with a radiopaque viscous hydrogel spacer showed unaffected long-term bowel QoL in patients with limitation of the target volume to the prostate.

INTRODUCTION

Rectal toxicity is considered as the dose-limiting toxicity for radiation therapy for prostate cancer [1] and the substantial risk for a patient in comparison to radical prostatectomy, as reported in various prospective studies in the past [2, 3]. The injection of a spacer between the prostate and anterior rectal wall creates a significant distance to the organ at risk and is thus able to decrease toxicity and prevent decreasing bowel quality of life [4]. Clinical spacer application numbers and the number of published studies has increased considerably in the last years [5, 6].

Efforts are made to improve hydrogel characteristics, including visibility in imaging and hydrogel injection. A radiopaque viscous hydrogel spacer (RVS, SpaceIT, Boston Scientific, Marlborough, USA) has been developed and evaluated in a first prospective study [7]. The first publication reported the hydrogel distribution, distances between the prostate and rectum and toxicity. The current subsequent analysis adds the available quality of life (QoL) results up to a long follow-up of >5 years after radiotherapy.

As this hydrogel is not injected as a fluid, placement can be effectively controlled during injection and also placed focally in a specific area, if required. In contrast, an initially fluid spacer (SpaceOAR, Boston Scientific, Marlborough, USA) spreads in a predetermined space that is usually opened during a hydrodissection [8]. Furthermore, the advantage of a radiopaque (iodinated) spacer is a good visibility in computed tomography (CT) for treatment planning and image guidance on the treatment table.

This is the first prospective phase II study evaluating QoL in prostate cancer radiotherapy after applying a radiopaque viscous hydrogel spacer. The aim of the study was to demonstrate unaffected long-term bowel QoL in comparison to baseline levels, independently from radiotherapy (RT) treatment technique. The aim is based on prior experience with the initially fluid spacer (SpaceOAR) [5, 9], preserving bowel QoL independently of the actual treatment concept. While introducing a new spacer, it is

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important to demonstrate that the foreign body also does not lead to harm for the patients. Continuation to a larger study was initially planned after favourable experience in an initial smaller group of patients.

MATERIALS AND METHODS

Quality of life analysis

Consecutive patients with a histologically confirmed diagnosis of a cT1-2N0M0 prostate cancer (without extracapsular extension) in two radiotherapy centers were included in this prospective study. The study was approved by the RWTH Aachen University ethics committee (acceptance number and date: EK 002/17; 28th February 2017).

The EPIC (Expanded Prostate Cancer Index Composite)[10,11] questionnaire was used for QoL assessment, comprising 50 items concerning urinary, bowel, sexual and hormonal domains. Each domain includes a function and bother subdomain. The scores are transformed to a 0 to 100 scale – higher scores represent a better QoL. A mean score change of >5 points is defined as clinically relevant (5-10 = little; 10-20 = moderate; >20 = large changes) [12]. A positive change corresponds to worse, a positive change to improving QoL.

Patients responded before RT, at the last day of RT, 3 months, >12 months and >60 months after RT. Patients responding to the baseline questionnaire and at least one follow-up questionnaire were included in this analysis (n=27). This analysis supplements a prior publication that reported the hydrogel distribution and toxicity results [7].

A significant QoL change was defined as a statistically significant mean change >5 points in comparison to baseline. Thus, the aim of the study was to demonstrate that the long-term mean score change in the bowel domain relative to the baseline score remains <5 points independently from the radiotherapy technique (control group for study group = same patients after group before treatment).

Spacer injection and treatment

RVS is a synthetic hydrogel consisting primarily of water and iodinated cross-linked polyethylene glycol (PEG). A total volume of 10ml was injected in each patient (figure 1). It was delivered in sterile pre-filled glass syringes. The glass syringe was attached to a sterile plastic syringe via a luer-luer connector. The entire volume has been moved back and forth from the glass syringe to the plastic syringe five times, ending up in the plastic syringe ready for injection.

The injection was performed under local anaesthesia in all patients under TRUS (transrectal ultrasound) guidance. After hydrodissection of the space between prostate and anterior rectal wall, the needle was positioned at the base and moved towards the apex during the injection of each syringe, respectively. The three 3ml syringes were injected medially, at the left and right lobes, respectively. Finally, a last syringe was applied to optimise the result individually.

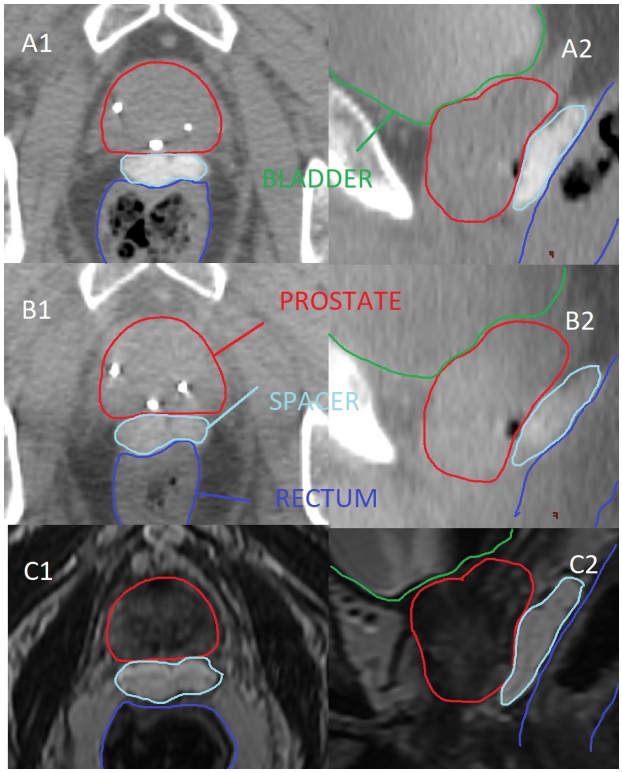

Figure 1. Spacer imaging in a treatment planning CT (**A1**-axial; **A2**-sagittal), a cone beam CT (**B1**-axial; **B2**-sagittal) and aT2 weighted MRI (**C1**-axial; **C2**-sagittal).

The aim was to prevent significant QoL changes, irrespective of the radiotherapy concept. Thus, patients were treated with standard radiation doses and fractionations, as recommended by international treatment guidelines, including different fractionation concepts and brachytherapy as a boost [13].

External beam radiotherapy concepts included intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT), applying 6 MeV photons. Radiotherapy concepts included normal fractionation with 1.8-2 Gy fractions up to a total dose of 76-80Gy (n=10), hypofractionation with 3-3.1 Gy fractions up to a total dose of 60-62Gy (n=12) and a combined external beam radiotherapy (2 Gy fractions up to 50 Gy) with a high dose rate (HDR) brachytherapy boost (two 9Gy fractions to the prostate encompassing isodose; n=5). An Ir-192 source was used for HDR brachytherapy. Pelvic node radiotherapy was also allowed (1.8-2 Gy fractions up to 50-50.4 Gy; n=6).

Statistical analysis

The IBM SPSS 29.0 (New York, USA) software was used for statistical analysis. The Mann-Whitney U-

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test was applied to determine differences between continuous patient characteristics, including quality of life score differences between patient subgroups. The chi-square test served to compare categorical variables. The Wilcoxon's matched-pairs test was applied to determine longitudinal changes within a specific subgroup. All p-values reported are two-sided, $p<0.05$ is considered significant.

RESULTS

Patients included in this analysis had a median age of 73 (range 60-83) years. Median prostate-specific antigen (PSA) before RT was 8.7 (range 4.4-77) ng/ml. Gleason score was 6, 7 and ≥8 in 22%, 56% and 22%. Patients were classified as low (no risk factors: PSA<10ng/ml, T-stage ≤T2a, Gleason score 6), intermediate (one risk factor: PSA 10-20ng/ml or Gleason score 7 or T-stage T2b/c) and high risk (two risk factors or PSA >20ng/ml or Gleason score >7) patients in 15%, 30% and 55% (table 1).

The largest urinary and bowel domain changes were found at the end of RT (table 2; ≥10 points mean change in the function and bother subdomains, respectively, p≤0.01). Significant urinary changes in comparison to baseline were not detected during further follow-up, with a mean difference of +1 and -3 points for urinary function and bother after >60 months, respectively. Thus, neither a clinically nor a statistically negative long-term urinary QoL effect has been found in our patient group.

Bowel function subdomain changes remained without a significant difference in comparison to baseline at all evaluation points in time (<3 points, respectively). In the bother subdomain, mean long-term changes were >5 points and statistically significant (8 and 6 points after >12 and >60 months). In contrast to patients after pelvic node RT, the difference after >60 months was <5 points for patients after prostate only RT (mean 12 vs. 4 points; median 12 vs. 0 points).

Table 1. Patient characteristics.

median patient age (range)	**73 (60-83) years**
median PSA (range	8.7 (4.4-77) ng/ml
Gleason score 6 / 7 / ≥8	22% / 56% / 22%
low / intermediate / high risk	15% / 30% / 55%
normal fractionation (1.8-2Gy) / hypofractionation (3-3.1Gy) / combined external beam with HDR brachytherapy	37% / 44% / 19%
prostate only / prostate with pelvic nodes	78% / 22%

PSA: prostate-specific antigen; HDR: high dose rate

Table 2. Quality of life changes after radiotherapy (mean; quartiles in brackets) in comparison to baseline levels before treatment (positive change corresponds to decreasing - worse - quality of life scores).

		prostate only	prostate and pelvic nodes	all patients
baseline urinary function score		93 (89;100;100)	98 (94;100;100)	94 (93;100;100)
urinary function score changes	end of RT	**12 (0;8;28)**	15 (0;8;37)	**13 (0;8;28)**
	3 months after RT	3 (-10;0;17)	-1 (-4;0;0)	2 (-6;0;0)
	>12 months after RT	-1 (-8;0;3)	2 (0;0;6)	0 (-1;0;6)
	>60 months after RT	2 (-3;0;3)	-1 (-4;0;0)	1 (-3;0;0)
baseline urinary bother score		85 (68;95;100)	82 (71;84;93)	85 (67;91;100)
urinary bother score changes	end of RT	**17 (0;18;29)**	16 (6;14;28)	**17 (3;18;29)**
	3 months after RT	6 (0;6;13)	-4 (-13;-4;6)	4 (-6;4;10)
	>12 months after RT	-10 (-30;3;11)	3 (-9;0;17)	-5 (-18;2;9)
	>60 months after RT	-4 (-14;0;0)	-2 (-11;2;4)	-3 (-9;0;2)
baseline bowel funtion score		93 (87;95;100)	92 (87;92;97)	93 (88;95;100)
bowel function score changes	end of RT	**10 (0;4;23)**	9 (0;8;18)	**10 (0;4;21)**
	3 months after RT	0 (-2;0;4)	4 (1;4;7)	1 (0;0;4)
	>12 months after RT	1 (-5;2;6)	4 (-6;0;15)	2 (-4;0;4)
	>60 months after RT	1 (-8;0;4)	10 (1;8;20)	3 (-6;0;8)
baseline bowel bother score		95 (95;100;100)	95 (92;98;100)	95 (96;100;100)
bowel bother score changes	end of RT	**15 (0;0;29)**	12 (4;14;17)	**14 (0;0;21)**
	3 months after RT	4 (0;0;5)	4 (0;2;9)	4 (0;0;5)
	>12 months after RT	**8 (0;1;10)**	8 (-4;4;28)	**8 (0;2;11)**
	>60 months after RT	4 (0;0;7)	12 (1;12;24)	6 (0;0;13)

RT: radiotherapy; statistically significant changes (p<0.05) in bold numbers.

Table 3. Exemplary urinary and bowel items.

item	before RT (%)	end of RT (%)	3 months after RT (%)	>12 months after RT (%)	>60 months after RT (%)
pain or burning on urination ≥once a day	0	**35**	12	0	0
big or moderate problem with urinary funtion overall	19	**57**	41	20	24
rectal urgency ≥once a day	15	**41**	12	20	6
loose or liquid stools ≥about half the time	4	**30**	12	20	6
bloody stools ≥rarely	8	4	0	13	12
crampy pain in the abdomen or rectum ≥once a day	4	0	0	7	0
big or moderate problem with bowel habits overall	0	**22**	6	7	0

RT: radiotherapy; statistically significant changes (p<0.05) in bold numbers.

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Exemplary urinary and bowel items with the respective patient percentages at specific intervals are presented in table 3, again demonstrating statistically significant changes at the end of RT in the urinary and bowel domains. In the complete patient group, only 0-1 patients reported big or moderate bother in any of the seven bowel bother items in evaluations 3 months or later after RT, a similar rate as before RT. No patient reported big or moderate bother with bowel habits overall.

DISCUSSION

This study reports the first prospective quality of life evaluation in prostate cancer patients treated with a radiopaque viscous hydrogel spacer. This experience serves as a start before the design of a larger prospective randomized study. This specific hydrogel was initially designed as a tissue marker and was available as a tissue marker and spacer in the last decade [7, 14]. It has not been commercially available in the last years. Therefore, quality of life results >5 years after radiotherapy applying the radiopaque viscous hydrogel spacer from a larger group of patients will not be available in the next 5 years.

Experience with other spacer materials, as hyaluronic acid or biodegradable balloon, has also been published in the last years. However, results are only limited to a follow-up of only a few months [15, 16].

The injection procedure and resulting spacer distribution with the RVS have been already reported, also in comparison with a patient population with an initially fluid spacer [7]. This comparison showed a significantly larger distance at the prostate base, with a comparable gel symmetry (right vs. left from midline). There were no signs of spacer migration during the radiotherapy treatment. No procedure-related toxicities and only grade 1 gastrointestinal toxicities were observed. The median rectum volume percentage within the 90% isodose was only 3% (interquartile range 1.5-4.5%).

Improvement of radiotherapy treatment techniques in the last decades resulted to improved protection of organs at risk [17, 18]. We allowed many different radiotherapy treatment concepts, as the aim was to prevent rectal toxicity and demonstrate no detrimental effects on bowel QoL irrespective of the treatment concept – with no clinically or statistically significant change in relation to the baseline levels before treatment, as previously reported using the initially fluid spacer SpaceOAR [19, 20]. The aim of the study was well reached for patients treated without pelvic nodes. As a spacer placement can only protect the anterior rectal wall in the vicinity of the prostate and not more proximal bowel parts, in particular the small bowel or sigmoid inside the pelvis, some moderate negative long-term bowel QoL effects were detectable for patients with RT of pelvic nodes. A larger effect on bowel QoL resulting from whole pelvic versus prostate only radiotherapy is well known from prior publications [21, 22].

Prior studies with an initially fluid hydrogel spacer - including a randomized controlled study - have already been published in the recent years, well demonstrating a significant advantage in comparison to patients treated conventionally without a spacer [19, 23, 24]. An advantage could not be shown for acute bowel toxicity. A recently published analysis has also shown significant advantages for sexual quality of life, including the percentage of patients with preserved erections firm enough for intercourse [5]. In the last years, a new radiopaque hydrogel spacer has been developed (SpaceOAR Vue™) and well established in clinical practice [25]. Short-term experience in a randomized study with a hyaluronic acid spacer (also injected as viscous gel, but not radiopaque) have been also recently published [15].

The RVS evaluated in this study has the advantage of being very well visible in computed tomography (CT) and cone-beam CT, thus with advantages for treatment planning and image-guidance during treatment. Furthermore, there is an improved placement control, though the injection requires more time and attention during the injection process. Focal injections of smaller amounts are possible, if target volumes are limited to only parts of the prostate for focal radiotherapy or brachytherapy or seminal vesicles, as recently demonstrated in specific cases [14].

CONCLUSION

The first QoL analysis after RT with a radiopaque viscous hydrogel spacer showed unaffected long-term bowel QoL in patients with limitation of the target volume to the prostate. A larger randomized phase III study (ClinicalTrials.gov ID NCT06451614, SpaceIT Hydrogel System for Perirectal Spacing) has shortly started recruiting patients.

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Conflict of interest: Michael Pinkawa and Hathal Haddad received speaker honoraria from Boston Scientific. The authors declare no other conflicts of interest.

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Ethical considerations: The study was approved by the RWTH Aachen University ethics committee (acceptance number and date: EK 002/17; 28th February 2017).

Author contribution: M.P. designed and conceived the study; M.P, Ha.Ha., Ho.He. and M.S collected and analyzed the data; M.P. prepared the figure and

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drafted the manuscript; Ha.Ha., A.R., S.T., Ho.He. and M.S. reviewed the manuscript. All authors read and approved the final manuscript.

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