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Scientific Letter

Quality of Life After Radiation Therapy for Prostate Cancer With a Hydrogel Spacer: 5-Year Results

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Summary

Spacers are increasingly placed between the prostate and rectal wall before prostate cancer radiation therapy. Long-term clinical results are needed to better define a possible benefit for patients. The first 5-year quality of life results in a group of prostate cancer patients treated with a hydrogel spacer demonstrate excellent treatment tolerability, in particular regarding bowel problems, superior to the results of a control group treated conventionally.

Purpose: To evaluate quality of life changes up to 5 years after prostate cancer radiation therapy (RT) with a hydrogel spacer.

Methods and Materials: In the years 2010 to 2011, 114 patients received external beam radiation therapy to the prostate; 54 patients were selected for a hydrogel injection before the beginning of RT. Treatment was performed applying fractions of 2 Gy up to a total dose of 76 Gy (n = 96) or 78 Gy (n = 18, all with hydrogel). Patients were surveyed before RT; at the last day of RT; and a median time of 2 months, 17 months, and 63 months after RT using a validated questionnaire (Expanded Prostate Cancer Index Composite). A mean score change of >5 points was defined as clinically relevant.

Results: For patients treated with a hydrogel spacer, mean bowel function and bother score changes of >5 points in comparison with baseline levels were found only at the end of RT (10-15 points; $P<.01$). No spacer patient reported moderate or big problems with his bowel habits overall. Mean bother score changes of 21 points at the end of RT, 8 points at 2 months, 7 points at 17 months, and 6 points at 63 months after RT were found for patients treated without a spacer. A bowel bother score change >10 points was found in 6% versus 32% ($P<.01$) at 17 months and in 5% versus 14% ($P=.2$) at 63 months with versus without a spacer.

Conclusions: The first 5-year quality of life results in a group of prostate cancer patients treated with a hydrogel spacer demonstrate excellent treatment tolerability, in particular regarding bowel problems. Further studies with dose-escalated or re-irradiation concepts can be encouraged.

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Introduction

Radiation therapy or radical prostatectomy are the curative treatment options for localized prostate cancer. In a recently published randomized study, metastases and overall survival rates have been shown to be comparable (1). Applying the EPIC (Expanded Prostate Cancer Index Composite), external beam radiation therapy proved to be favorable in the urinary and sexual domains (2). However, a disadvantage resulted in the bowel domain, as in several previous comparative studies (3, 4).

Because the anterior rectal wall is located close to the prostate, it is commonly included in the high-dose volume. Biodegradable spacers can be injected or inserted between the prostate and anterior rectal wall to achieve a distance of approximately 1.0 to 1.5 cm between the prostate and rectum. Several studies have reported well-tolerated injection procedures and radiation therapy (RT) treatments (5). Apart from considerable reduction of rectal dose, a prospective, randomized trial has shown a reduction of rectal toxicity after hydrogel injection in patients undergoing RT for prostate cancer (6, 7).

Long-term clinical results are needed to better define a possible benefit for patients. The aim of this analysis was to evaluate quality of life changes up to 5 years after RT for prostate cancer with a hydrogel spacer.

Methods and Materials

In the years 2010 to 2011, 114 patients received external beam radiation therapy to the prostate without pelvic lymph nodes in our department. Depending on the patient's and responsible radiation oncologist's preference, 54 patients were selected for a hydrogel injection before the beginning of RT. The injection of 10 mL hydrogel (SpaceOAR System, Augmenix, Waltham, MA) was performed under transrectal ultrasound guidance after dissecting the space between prostate and rectum with a saline/lidocaine solution under local anaesthesia, as explained in detail in prior publications (8).

Treatment plans were based on a computed tomography scan in the supine position with a full bladder, within 3 to 5 days after hydrogel injection. Additionally, T2-weighted magnetic resonance imaging scans were performed for image fusion in 27 patients after hydrogel injections (initial experience). For the planning target volume, 8-mm lateral and anterior, 5-mm superior and inferior, and 4-mm posterior margins were added to the clinical target volume (corresponding to prostate with or without seminal vesicles) contours. Treatment was performed with a 5-field intensity modulated radiation therapy technique (180°, 105°, 45°, 315°, 255° gantry angles), applying fractions of 2 Gy up to a total dose of 76 Gy (n=96) or 78 Gy (n=18, all with hydrogel). The same objectives and constraints were used for inverse intensity modulated radiation therapy treatment planning for all patients: maximum rectum V_{50} = 50%, maximum rectum V_{70} = 20% (constraint: 76 Gy maximum rectal dose), maximum bladder V_{55} = 50%, maximum bladder V_{70} = 30%. Ultrasound-based image guidance was applied before each fraction.

Patients were surveyed prospectively before RT; at the last day of RT; and a median time of 2 (range, 1-3) months, 17 (range, 12-23) months, and 63 (range, 55-70) months after RT using the EPIC questionnaire (9); comprising 50 items concerning urinary, bowel, sexual, and hormonal domains); with 91, 82, 79, 106, and 84 responses (including 50, 51, 48, 51, and 41 patients with hydrogel), respectively. The total number of questionnaire pairs to analyze changes relative to baseline levels before treatment was 80, 77, 85, and 65 at the last day of RT; and 2 months, 17 months, and 63 months after RT, respectively (including 49, 46, 47, and 37 patients with hydrogel). The multi-item scale scores were transformed linearly to a 0 to 100 scale, with higher scores representing better quality of life. A mean score change of >5 points was defined as clinically relevant: 5 to 10 as "little," 10 to 20 as "moderate," and >20 as "very much" changed (10).

IBM SPSS 22.0 (Armonk, NY) software was used for statistical analysis. The Mann-Whitney *U* test was applied to determine differences between continuous patient characteristics, including quality of life score differences between patient subgroups. The χ^2 test served to compare categorical variables. The Wilcoxon matched-pairs test was applied to determine longitudinal changes within a specific subgroup. All *P* values reported are 2-sided; $P<.05$ is considered significant.

Results

Baseline patient characteristics of patients treated with a spacer were similar to those of patients who were treated without a spacer in the same time period. Apart from a significantly lower dose to the rectum for patients with a spacer, all *P* values were above the level of statistical significance (Table 1). Mean bowel function and bother score changes of >5 points in comparison with baseline levels before treatment were found only at the end of RT (10-15 points; $P<.01$) for patients treated with a hydrogel spacer. Mean long-term urinary and bowel domain scores hardly differed from baseline in the spacer group (<2 points). No spacer patient reported a moderate or big problem with his bowel habits overall. A single patient with a hydrogel spacer reported an invasive bowel procedure within the follow-up period (a polypectomy).

Bowel domain score changes were higher (statistically not significant) in comparison with the patient group with a spacer, with mean bother score changes of 21 points at the end of RT, 8 points at 2 months, 7 points at 17 months, and 6 points at 63 months after RT. Statistically significant differences were found comparing bowel domain scores 17 months after RT ($P=.01$) and specific items 17 months and 63 months after RT (Table 2). Five non-spacer patients reported an invasive bowel procedure: 2 polypectomies, 2 sclerotherapies of hemorrhoids, and a single endoscopic

Table 1 Baseline patient characteristics

Characteristic	With spacer (n=54)	Without spacer (n=60)
Patient age (y), median (range)	73 (56-82)	73 (53-84)
PTV (cm^3), median (range)	126 (37-335)	123 (36-254)
PSA (ng/mL), median (range)	7.6 (2.3-83)	7.1 (1.8-94)
Low/intermediate/high-risk patients, %	35/41/24	32/47/22
Bowel function score before RT, mean (quartiles)	96 (89;96;100)	96 (89;96;100)
Bowel bother score before RT, mean (quartiles)	100 (93;100;100)	96 (90;96;100)
Most frequent comorbidities (%)		
Hypertension	35	28
Coronary heart disease	15	20
Diabetes	7	7
Mean (quartiles) dose to bladder		
Percentage of volume inside 90% isodose	16 (8;12;23)	14 (6;12;20)
Percentage of volume inside 70% isodose	28 (16;24;40)	27 (15;25;32)
Mean (quartiles) dose to rectum		
Percentage of volume inside 90% isodose	4 (0;2;7)	13 (6;12;16)*
Percentage of volume inside 70% isodose	20 (12;18;30)	32 (24;31;38)*

Abbreviations: PSA = prostate-specific antigen; PTV = planning target volume; RT = radiation therapy.
* $P<.01$ comparing patients with versus without a spacer.

coagulation of a rectal bleeding. A bowel bother score change >10 points was found in 6% versus 32% ($P<.01$) at 17 months and in 5% versus 14% ($P=.2$) at 63 months with versus without a spacer.

Sexual bother score changes tended to be smaller in the patient group with a spacer. At the time of the last questionnaire, 24% (with spacer) versus 3% (without spacer) reported erections firm enough for intercourse ($P<.01$).

Discussion

Because the anterior rectal wall is located at the posterior prostate border, it is exposed to high doses even with modern intensity modulated and image guidance techniques, resulting in a risk of acute and late rectal toxicities (11). A spacer increases the distance between the prostate and rectum over a period of several weeks.

The dosimetric advantage, protecting the rectum from high dose levels, and the stability for the treatment duration have been clearly shown in this study and in prior studies evaluating a spacer application (12, 13). Several studies have been published about the injection procedure and toxicity during RT or a few months after RT (8, 14). In a larger series of 258 patients from different centers, injection-related grade 2 toxicities were reported in 5 cases (2%), most frequently a rectal wall penetration of the hydrogel (15). Other studies also reported grade 3 events, such as rectal ulcerations or fistulas (16). These might be associated with the injection technique or RT technique, for example in hypofractionated carbon ion or proton radiation therapy (14, 16).

Table 2 Quality of life 1 and 5 years after radiation therapy

Variable	With spacer	Without spacer	*P*
1.5 years after RT			
Mean (quartiles) urinary bother score change	−2 (−7;0;4)	−3 (−11;−4;4)	.49
Mean (quartiles) bowel bother score change	−1 (0;0;0)	7 (−4;0;14)	.13
Mean (quartiles) sexual bother score	13 (0;6;31)	18 (0;19;42)	.28
Moderate/big problem with bowel urgency %	0	13	<.01
Moderate/big problem with losing control of stools %	0	9	.03
Moderate/big problem with bowel habits overall %	0	17	<.01
5 years after RT			
Mean (quartiles) urinary bother score change	0 (−5;0;7)	−3 (−9;−4;4)	.22
Mean (quartiles) bowel bother score change	1 (0;0;4)	6 (−4;0;11)	.99
Mean (quartiles) sexual bother score	21 (0;9;39)	28 (−6;31;75)	.77
Moderate/big problem with bowel urgency %	0	14	.01
Moderate/big problem with losing control of stools %	0	7	.09
Moderate/big problem with bowel habits overall %	0	7	.08

Abbreviation as in Table 1.
Positive number corresponds to decreasing score.

Cost-effectiveness of hydrogel injection is a controversial issue in times of emerging new treatments and increasing health care costs. Despite significant advantages of hydrogel, conventional RT is also well tolerated for the vast majority of our patients. Published studies have compared the cost of hydrogel injection in comparison with the cost of rectal toxicities. Vanneste et al (17) found the spacer to be cost-effective owing to less severe rectal toxicities and cost reductions in the management of rectal side effects. Hutchinson et al (18) concluded cost-effectiveness of hydrogel use for patients treated with high-dose stereotactic RT, but cost increases for conformal RT.

Because this is a retrospective cohort study with a heterogeneous patient population, a bias cannot be excluded for unknown or non-evaluated baseline characteristics. The current best evidence is a randomized study, with recently reported final 3-year results (7), also using the EPIC questionnaire with the benefit of giving us information about the most important effects of prostate cancer treatment from the patient's perspective. The clinical comparison with patients treated without a spacer reveals hardly any difference in the acute phase in all published studies, but statistically significant long-term advantages of the spacer, with lower numbers of rectal toxicities and better bowel quality of life (6, 7, 19). The most important result is a long-term bowel quality of life that does not differ from the baseline level before treatment, which is an important aim of our treatment. This aim was reached in the randomized study (6, 7), as well as in our initial experience after a follow-up period of 5 years, supporting the results of the randomized study in an independent single-center experience in a smaller patient group, but a longer follow-up period. The proportion of patients with at least a 10-point decline of bowel scores was significantly smaller for patients with a spacer in the randomized study, with percentages comparable to our study (5% vs 21% after 3 years; $P = .02$). A moderate or big problem with bowel movements has not been reported in the spacer group after 1 to 2 or after 5 to 6 years following treatment in our study. The favorable experience is encouraging for the design of further larger studies with hypofractionated or dose-escalated or re-irradiation concepts.

References

1. Hamdy FC, Donovan JL, Lane JA, et al. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med* 2016;375:1415-1424.
2. Donovan JL, Hamdy FC, Lane JA, et al. Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *N Engl J Med* 2016;375:1425-1437.
3. Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med* 2008;358:1250-1261.
4. Resnick MJ, Koyama T, Fan KH, et al. Long-term functional outcomes after treatment for localized prostate cancer. *N Engl J Med* 2013;368:436-445.
5. Pinkawa M. Current role of spacers for prostate cancer radiotherapy. *World J Clin Oncol* 2015;6:189-193.
6. Mariados N, Sylvester J, Shah D, et al. Hydrogel spacer prospective multicenter randomized controlled pivotal trial: Dosimetric and clinical effects of perirectal spacer application in men undergoing prostate image guided intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys* 2015;92:971-977.
7. Hamstra DA, Mariados N, Sylvester J, et al. Continued benefit to rectal separation for prostate radiation therapy: Final results of a phase III trial. *Int J Radiat Oncol Biol Phys* 2017;97:976-985.
8. Hatiboglu G, Pinkawa M, Vallee JP, et al. Application technique: Placement of a prostate-rectum spacer in men undergoing prostate radiation therapy. *BJU Int* 2012;110(11 Pt B):E647-E652.
9. Wei JT, Dunn RL, Litwin MS, et al. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. *Urology* 2000;56:899-905.
10. Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998;16:139-144.
11. Zelefsky MJ, Levin EJ, Hunt M, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;70:1124-1129.
12. Song DY, Herfarth KK, Uhl M, et al. A multi-institutional clinical trial of rectal dose reduction via injected polyethylene-glycol hydrogel during intensity modulated radiation therapy for prostate cancer: Analysis of dosimetric outcomes. *Int J Radiat Oncol Biol Phys* 2013;87:81-87.
13. Pinkawa M, Piroth MD, Holy R, et al. Spacer stability and prostate position variability during radiotherapy for prostate cancer applying a hydrogel to protect the rectal wall. *Radiother Oncol* 2013;106:220-224.
14. Uhl M, van Triest B, Eble MJ, et al. Low rectal toxicity after dose escalated IMRT treatment of prostate cancer using an absorbable hydrogel for increasing and maintaining space between the rectum and prostate: Results of a multi-institutional phase II trial. *Radiother Oncol* 2013;106:215-219.
15. Muller AC, Mischinger J, Klotz T, et al. Interdisciplinary consensus statement on indication and application of a hydrogel spacer for prostate radiotherapy based on experience in more than 250 patients. *Radiol Oncol* 2016;50:329-336.
16. Habl G, Uhl M, Katayama S, et al. Acute toxicity and quality of life in patients with prostate cancer treated with protons or carbon ions in a prospective randomized phase II study—the IPI Trial. *Int J Radiat Oncol Biol Phys* 2016;95:435-443.
17. Vanneste BG, Pijls-Johannesma M, Van De Voorde L, et al. Spacers in radiotherapy treatment of prostate cancer: Is reduction of toxicity cost-effective? *Radiother Oncol* 2015;114:276-281.
18. Hutchinson RC, Sundaram V, Folkert M, et al. Decision analysis model evaluating the cost of a temporary hydrogel rectal spacer before prostate radiation therapy to reduce the incidence of rectal complications. *Urol Oncol* 2016;34:e19-e26.
19. Pinkawa M, Berneking V, Konig L, et al. Hydrogel injection reduces rectal toxicity after radiotherapy for localized prostate cancer. *Strahlenther Onkol* 2017;193:22-28.