BJU Int 2020; **126:** 367–372 doi:10.1111/bju.15097

BJUI
BJU International

Original Article

Long-term follow-up after radiotherapy for prostate cancer with and without rectal hydrogel spacer: a pooled prospective evaluation of bowel-associated quality of life

Zachary A. Seymour[1,2], Daniel A. Hamstra[1,2], Stephanie Daignault-Newton[3], Walter Bosch[4], Jeffery Michalski[4], Hiram A. Gay[4] and Michael Pinkawa[5]

[1]Department of Radiation Oncology, Beaumont Health, Dearborn, [2]Oakland University William Beaumont School of Medicine, Rochester, [3]Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, [4]Department of Radiation Oncology and School of Medicine, Washington University, St. Louis, MO, USA, and [5]Department of Radiotherapy, RWTH Aachen University, Aachen, Germany

Presentation: Poster Presentation ASCO GU 2019, San Francisco, CA.

Z.A.S and D.A.H. equal contribution to this publication.

Objective

To evaluate the long-term bowel-associated quality of life (QOL) in men after radiotherapy (RT) for prostate cancer with and without the use of rectal hydrogel spacer.

Patients and Methods

The patients' QOL was examined using the Expanded Prostate Cancer Index Composite (EPIC) and mean changes from baseline in EPIC domains were evaluated. A total of 215 patients from a randomised multi-institutional trial of RT, with or without hydrogel spacer, with a QOL endpoint were pooled with 165 non-randomised patients from a single institution with prospective QOL collection in patients with or without hydrogel spacer. The proportions of men with minimally important differences (MIDs) relative to pre-treatment baseline in the bowel domain were tested using repeated measure logistic models with a pre-specified threshold for clinically significant declines (≥5 equivalent to MIDx1 and ≥10 equivalent to MIDx2).

Results

A total of 380 men were evaluated (64% with spacer and 36% without) with QOL data being available for 199 men with >24 months of follow-up [median (range) 39.5 (31–71.4) months]. Treatment with spacer was associated with less decline in average long-term bowel QOL (89.4 for control and 94.7 for spacer) with differences at >24 months meeting the threshold of a MID difference between cohorts (bowel score difference from baseline: control = −5.1, spacer = 0.3, difference = −5.4; $P < 0.001$). When evaluated over time men without spacer were more likely to have MIDx1 (5 points) declines in bowel QOL ($P = 0.01$). At long-term follow-up MIDx1 was 36% without spacer vs 14% with spacer ($P < 0.001$; odds ratio [OR] 3.5, 95% CI 1.7–6.9) while MIDx2 was seen in 19% vs 6% ($P = 0.008$; OR 3.6, 95% CI 1.4–9.1). The use of spacer was associated with less urgency with bowel movements ($P = 0.002$) and fewer loose stools ($P = 0.009$), as well as less bother with urgency ($P = 0.007$) and frequency of bowel movements ($P = 0.009$).

Conclusions

In this pooled analysis of QOL after prostate RT with up to 5 years of follow-up, use of a rectal spacer was associated with preservation of bowel QOL. This QOL benefit was preserved with long-term follow-up.

Keywords

radiotherapy, prostate cancer, patient-reported outcomes, toxicity, hydrogel spacer

Introduction

Radiotherapy (RT) for prostate cancer is associated with good results in terms of both limiting toxicity and maximising efficacy in men pursuing definitive therapy. Long-term results in terms of cancer-specific outcomes for surgery and RT appear similar. Patient-reported outcomes (PROs) appear to be divergent with worse bowel-related quality of life (QOL) with prostate-directed RT [1]. Continued improvements in image guidance and intensity modulation have allowed for more targeted modern RT delivery, utilising both smaller margins and higher doses, which may theoretically lead to better PROs. This approach has minimised the dose to many surrounding organs at risk, except for the immediately adjacent plexus of nerves, vessels, and the anterior rectal wall.

A rectal spacer hydrogel is available to provide a physical barrier between the high dose immediately adjacent to the prostate gland and the rectum. Data have been analysed from several series, prospective and retrospective, to assess for differences in toxicity and patient-reported QOL, but the reports to date have been with limited follow-up duration [2,3]. It was unclear if gains in mid-term QOL with the rectal spacer would be maintained or only delay declines in PROs.

The Expanded Prostate Cancer Index Composite (EPIC) is a standardised and validated measure of QOL for patients with prostate cancer. The EPIC bowel domain consists of bowel function, bowel bother, and a composite overall QOL evaluation. Initially within the literature were two series, with and without hydrogel spacer, in men receiving RT; however, limited follow-up was evaluable at ≥24 months in either cohort, and therefore reduced the capacity to evaluate QOL beyond this initial follow-up period. Presented here is a pooled analysis of these two series of hydrogel-rectal-spacer patient series with longer-term follow-up of bowel-related QOL: a prospective Phase III multi-centred randomised trial and a prospective non-randomised single-institution analysis of patients sequentially treated with or without a rectal hydrogel spacer [2,3].

Patients and Methods

Patient Selection and Treatment Parameters

The details of the Phase III trial and non-randomised patients were previously reported [3,4]. Men with National Comprehensive Cancer Network determined low- or intermediate-risk prostate cancer and a Zubrod Performance Status of 0 to 1 were enrolled in a multi-institutional Institutional Review Board-approved single-blind Phase III trial (ClinicalTrials.gov Identifier: NCT01538628) from 20 separate institutions. The exclusion criteria included: prostate volume ≥80 mL, extraprostatic extension, >50% positive biopsy cores, previous or planned use of androgen-deprivation therapy, and/or previous treatment of prostate cancer. The patients were randomised 2:1 to the spacer or control group, with all men receiving fiducial markers for image-guided RT. The patients were unaware of the treatment allocation and had the fiducial markers or markers plus the hydrogel spacer placed without knowing to which treatment they had been randomised. MRI-based planning was used, with the post-fiducial marker CT scan fused with the MRI scan. The RT plans were evaluated by an independent core laboratory before treatment for compliance to the protocol guidelines and determination of the dosimetric endpoints. The clinical target volume (CTV) was the prostate with or without the seminal vesicles at the physician's discretion. A planning target volume (PTV) margin of 5–10 mm was used. The RT dose was 79.2 Gy in 1.8-Gy daily fractions, delivered 5-days weekly. Based upon previously published dosimetric analysis, rectal dose constraints were all less than rectal volume receiving 50% of the dose (V_{50}) of 50% and rectum V_{70} of 20%, regardless of the presence of rectal spacer [2]. CT-based daily image guidance was used for RT delivery with alignment to the fiducials.

In the non-randomised cohort, all 114 patients were treated from 2010 to 2011 with external beam RT to the prostate without pelvic lymph nodes. Treatment plans were based on a CT scan in the supine position with a full bladder, within 3–5 days after hydrogel spacer injection. Additionally, T2-weighted MRI scans were performed for image fusion in 27 patients after hydrogel spacer injections in the initial experience and then CT scans alone were used thereafter. For the PTV, 8-mm lateral and anterior, 5-mm superior and inferior, and 4-mm posterior margins were added to the CTV (corresponding to prostate with or without seminal vesicles) contours. Treatment was performed with a five-field intensity modulated RT to a total dose of 76 Gy (n = 96) or 78 Gy (n = 18, all with hydrogel spacer). The same objectives and constraints were used for inverse intensity modulated RT treatment planning for all patients: maximum rectum V_{50} = 50%, maximum rectum V_{70} = 20% [3]. Ultrasound-based image guidance was used before each fraction.

Patient-reported QOL was obtained before RT and at follow-up after RT using the EPIC score. The rectal portion consists of an overall bowel QOL, referred to as EPIC Bowel QOL score, as well as a subset scores for patient-reported Bowel Function and Bowel Bother. Practice patterns varied in each cohort in terms of follow-up. In the prospective randomised study, follow-up occurred every 3 months for 2 years and then every 6 months, while the non-randomised cohort obtained patient-reported QOL surveys before treatment, at the completion of RT, and at approximately median EPIC scores for 2, 17, and 63 months after treatment.

Overall, 380 of the treated men with baseline EPIC scores were evaluated. Specifically, 245 patients were treated with and 135 were treated without rectal spacer. At 12 months of

follow-up, 211 patients with and 88 patients without rectal spacer were evaluable for PROs by EPIC (an overall 78% response rate). Late follow-up at ≥24 months was available in 128 patients with and 72 patients without rectal spacer (an overall 53% response rate). In the patients with an evaluable 'late' EPIC questionnaire completion, the median (range) time was 40.9 (31.1–71.4) months from treatment.

Statistical Analysis

Demographic and patient characteristics were described between treatment groups and patient cohorts separately. Chi-square tests for stage and Gleason Grade, *t*-tests for age, and Wilcoxon rank tests for percentage of positive cores, were used. The EPIC was evaluated by overall EPIC Bowel QOL, Bowel Bother, and Bowel Function, as well as by each individual question within the bowel domain. Based on standard interpretation of the EPIC Bowel QOL, a 'significant' score change of 5 points was defined as a minimally important difference (MID) and scored as MIDx1 and a 'severe' score change of 10 points was considered a MIDx2 [5]. Due to alterations in follow-up patterns between cohorts, 'late' follow-up was defined as ≥24 months after treatment. The bowel-domain analysis of the individual items, reports proportions and Fisher's exact tests were used for comparison between treatment groups. Multiple comparison adjustments were not made, as these are only used to identify the areas of the bowel score that differ for descriptive purposes.

The bowel score differences from baseline were modelled using longitudinal repeated measures with interest in the effect of treatment differences over time (months since treatment that the EPIC questionnaire was completed). Treatment, months since treatment, and interaction effect were included in the model. Repeated measures within a patient used an autoregressive correlation structure. Treatment by month estimates and pairwise testing was done within the modelling framework. Each binary MID endpoint was presented with proportions and binomial CIs by treatment and questionnaire months. Analysis was performed using the Statistical Analysis System (SAS), version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient Baseline Characteristics

All evaluable baseline treatment characteristics shared by the two patient cohorts are listed in Table 1, with evaluation of differences in the baseline characteristics based on utilisation of hydrogel, and between randomised and non-randomised patient subsets. Baseline characteristics were similar between the groups with or without rectal hydrogel spacer, except for patients with hydrogel spacer being younger at the time of treatment. Comparing patients between the randomised and non-randomised cohorts, there were associations towards older patients, lower rates of cT2 Stage, more Gleason Grade 7, higher percentage of positive cores on diagnostic biopsy, worse baseline EPIC bowel function score. However, differences between the baseline EPIC differences were not clinically meaningful based on MID and overall bowel EPIC summary scores were not statistically or clinically different.

Patient-reported Bowel QOL

RT to the prostate with rectal hydrogel spacer was associated with less decline in mean long-term overall Bowel EPIC summary score for overall bowel QOL (89.4 for control and 94.7 for hydrogel spacer) with modelled differences at 1 year compared to baseline diverging statistically ($P = 0.005$, Fig. 1). Beyond this time-point, differences continued to diverge while remaining statistically different. At 24 months, differences between the control and hydrogel rectal spacer cohorts were meeting the threshold for a clinically meaningful difference (Bowel Score Difference from baseline: control = −5.1, spacer = 0.3, difference = −5.4; $P = 0.001$), as patients with hydrogel spacer appeared to have preserved baseline

Table 1 Baseline patient characteristics.

	Randomised prospective data		Non-randomised prospective data		P*	P†
	Hydrogel spacer	Control	Hydrogel Spacer	Control		
N	146	69	99	66		
Age, years, mean (SD)	65.9 (7.8)	67.3 (6.6)	70.6 (6.5)	71.8 (7.0)	**0.03**	**<0.001**
Stage T2+, *n* (%)	52 (36)	23 (33)	27 (27)	16 (24)	0.53	0.071
Grade 7+, *n* (%)	51 (35)	35 (51)	52 (53)	35 (53)	0.066	**0.014**
% of positive cores, mean (SD)	22.9 (12.7)	23.3 (15.3)	31.4 (25.3)	29.4 (19.6)	0.99	**0.011**
Prostate volume, mL, median (range)	50.9 (26.6–100.1)	59.1 (25.9–111.5)	51.5 (19–180)	55.0 (21–134)	0.15	0.081
Baseline Bowel EPIC domain, mean (SD)						
Bowel	93.4 (8.1)	94.5 (6.3)	94.3 (10.3)	92.9 (9.23)	0.66	0.27
Bowel Function,	92.7 (9.4)	92.9 (7.7)	94.4 (8.6)	93.0 (8.5)	0.24	**0.03**
Bowel Bother	94.1 (8.7)	96.0 (6.5)	94.2 (12.8)	92.6 (11.5)	0.96	**<0.001**

Statistically significant values denoted in bold. *P, hydrogel spacer vs control †P, randomised vs non-randomised.

Fig. 1 The mean bowel difference in EPIC bowel domain from baseline for patients with rectal spacer (blue) and without rectal spacer (red) overtime with the SD with pairwise *P* value at each evaluable time-point.

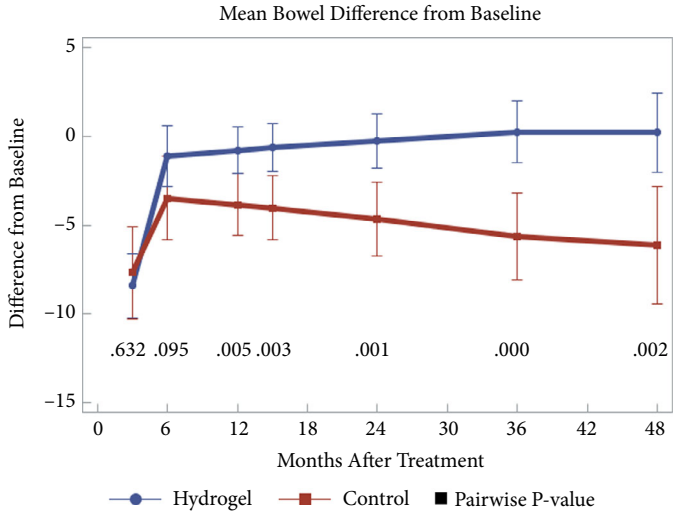
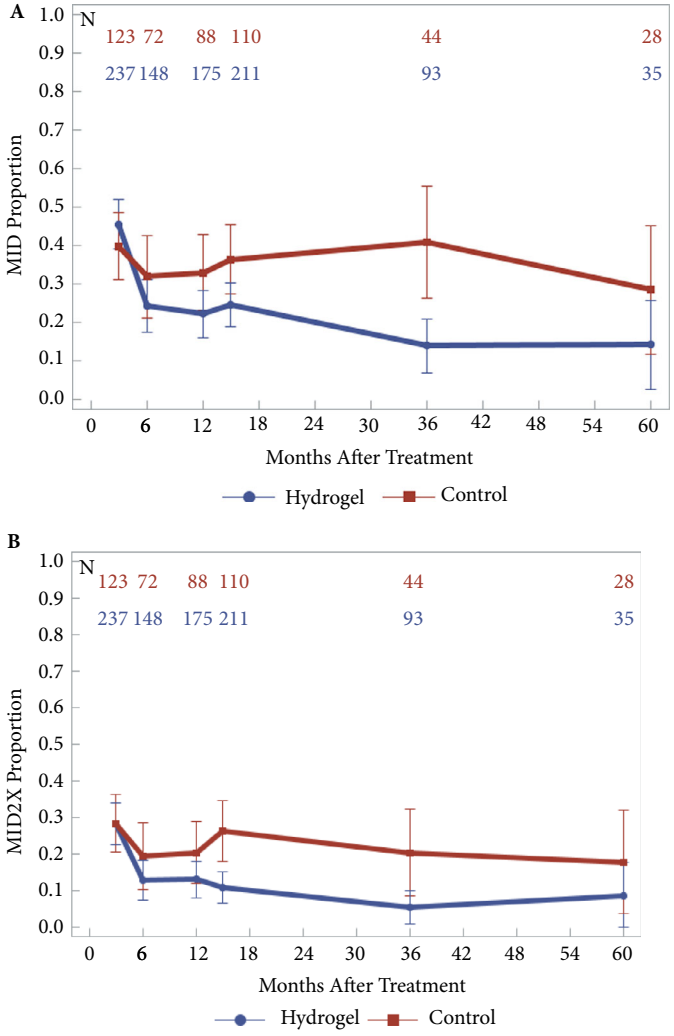


Fig. 2 Proportions of patients experiencing a minimally important clinical difference (MID) (**A**) and MIDx2 (**B**) in overall EPIC bowel QOL summary score, with (blue) and without rectal spacer (red), overtime with overall numbers of evaluable patients listed at each evaluated time-point.



QOL. This threshold for clinically significant decline was maintained for the MIDx1 difference between the cohorts up to 5 years of follow-up ($P = 0.002$). MIDx1 was trending towards significance at 12 months of follow-up ($P = 0.074$), with no difference in MIDx2. At 15 months of follow-up, MIDx1 and MIDx2 were both more frequent in patients without rectal spacer (MIDx1 at 15 months $P = 0.037$ and MIDx2 at 15 months $P < 0.001$). The model for bowel difference was associated with better PRO of bowel function ($P = 0.028$). When adjusting for multiple questionnaires being completed over time, it confirmed an increased risk of reduced bowel QOL overtime in patients without rectal spacer compared to those with spacer ($P < 0.001$).

Clinically relevant declines were noted beyond statistical differences and modelled data. At long-term follow-up the MIDx1 was 36% without spacer vs 14% with spacer ($P < 0.001$; odds ratio [OR] 3.5, 95% CI 1.7–6.9, Fig. 2), while MIDx2 was seen in 19% vs 6% ($P = 0.008$; OR 3.6, 95% CI 1.4–9.1). The differences in MIDx1 and MIDx2 between the hydrogel spacer and control groups corroborates statistical differences at later follow-up of >12 months (Fig. 2).

Specific aspects of bowel-related QOL were improved with rectal spacer placement relative to the controls (Table 2). Patients without hydrogel spacer were more likely to have significant declines at late follow-up in patient-reported function with more urgency with bowel movements ($P = 0.002$) and more loose stools ($P = 0.009$), as well as more bother with urgency ($P = 0.007$) and frequency of bowel movements ($P = 0.009$). There were also trends towards more bother from watery bowel movements ($P = 0.06$) and incontinence ($P = 0.08$) in men without hydrogel rectal spacer.

Evaluating differences in PROs by comparing randomised data to non-randomised data did not reveal any differences in patient-reported bowel QOL at any time points beyond 3 months of follow-up and even at that point were not clinically relevant of MIDx1 and potentially due to baseline statistical differences in the cohorts that were eventually minimised with the effect of hydrogel separation over time.

Discussion

The results of the present analysis conform within the broad reproducible data regarding rectal separation and improved physician-reported rates of toxicity and reduced declines in PROs. Declines in overall bowel QOL appeared to be increasing at least up to 3 years of follow-up after RT. This

Table 2 EPIC rectal QOL domain analysis over time by individual questions.

	Control				Hydrogel spacer			
	Baseline (*N* = 138)	3 months (*N* = 125)	15 months (*N* = 129)	36 months (*N* = 88)	Baseline (*N* = 248)	3 months (*N* = 241)	15 months (*N* = 215)	36 months (*N* = 134)
Bowel Function, %								
Urgency (≥1 day)	7.3	16	6.2	13.6*	10.1	21.2	7.9	2.2*
Leakage (≥1 day)	0	3.2	1.6	3.4	2	3.3	3.7	1.5
Loose stools (≥1 half)	10.1	16.7	13.2	13.6*	10.5	16.2	8.4	3.7*
Bloody stools (≥1 half)	0.7	3.2	6.2	1.1	0.8	1.7	0.9*	1.5
Painful stools (≥1 half)	2.2	8.7	3.8	2.3	2	5.8	1.9	0
Frequency (≥3 stools/day)	13.8	32.5	20.8	18.4	7.3	24.1	11.2*	12.7
Crampy pain (≥1 day)	1.5	5.6	3.1	2.3	2.4	5.9	1.9	2.2
Bowel Bother, %								
Urgency	2.9	8.9	5.4	8*	2.4	9.5	0.9*	0.8*
Frequency	1.5	7.4	3.9	5.7*	1.2	7.9	1.4	0*
Watery bowels	1.5	4.1	3.9	3.4	0.8	5	1.4	0
Incontinence	0	4.9	3.9	4.6	1.2	3.4	1.4	0.8
Bloody stools	0	1.6	3.9	1.1	0.4	0.8	1.4	0
Pain	0.7	0.8	3.1	1.1	1.6	4.2	0.5	0.8
Overall	2.9	7.2	7.7	5.8	2.4	9.5	2.8	1.5

Abbreviations: CTV, clinical target volume; EPIC, Expanded Prostate Cancer Index Composite; MID, minimally important difference; OR, odds ratio; PRO, patient-reported outcome; PTV, planning target volume; QOL, quality of life; RT, radiotherapy; V_{50}, rectal volume receiving 50% of the dose; V_{70}, rectal volume receiving 70% of the dose. $^{*}P < 0.05$.

appeared to mirror continued accumulation of MIDs in patient-reported bowel function from 12 to 36 months of follow-up, whereas MIDx2 did not appear to be substantially increased with increased follow-up beyond 12 months. This suggests that many more significant declines in bowel function occur in the mid-term of follow-up and do not recover. It is possible that continued decline in either group would be possible with additional follow-up, but the accumulation of MIDx1 events may suggest that continued decline with sufficient follow-up may ultimately increase late MIDx2 events. The natural history of these declines reinforce that these declines are real and not occurring in a significantly delayed fashion that would be limited to only patients who are long-term survivors.

Further follow-up is needed to assess continued QOL in these cohorts, but together this represents a preservation of bowel function with rectal spacer utilisation in the face of continued decline in patients treated with prostate-seminal vesicle only RT without a rectal spacer. The plans utilised in either the randomised or the non-randomised cohorts were quality RT plans by accepted standards, but the results of are important to place into context of the intervention [4].

With any intervention, there is a potential learning curve to both placement and understanding dosimetric feasibility. Given that this represents the first experience with rectal separation, these results may underrepresent differences in optimised plans with rectal spacers with adequate experience. While placement geometric evaluations have failed to provide hints at the ideal localisation of rectal separation and the PROSQA analysis allowed for optimisation of dosimetric constraints without rectal spacer, future dosimetric analysis within patients with rectal spacers will provide important information for practitioners [6].

Furthermore, no patients were found on subset analysis whom did not benefit from rectal separation with regards to rectal QOL. Prostate volume, pre-rectal gel placement dosimetry, distance of rectal separation, geometry of placement, and prior pelvic and/or abdominal surgery did not impact QOL in previous analyses [6,7]. All patients had such a significant decline in rectal dose receiving 70 Gy that all patients benefited from the spacer placement with relative declines of >70% across all patients. While there are limitations in a pooled analysis with regards to patient heterogeneity, as well as slight differences in treatment planning and follow-up regimens, it appears that no other planning technique or baseline characteristic would be able to modulate the risk of reductions in long-term QOL reported here, with perhaps the exception of brachytherapy or stereotactic RT with much smaller PTV margins.

Given the timeline to the clinically meaningful difference in PRO, essentially all patients treated without a rectal spacer will be at increased risk of these declines well within their lifetime. This may provide a rationale for utilisation of rectal spacers in patients with higher-risk disease rather than the favourable intermediate-risk cohorts evaluated here. Feasibility, albeit with at some risk of microscopic spread of a gel insertion in cases with significant micro- or macroscopic spread beyond the prostate, will have to be investigated in this higher-risk cohort. Prospective

evaluations of utilisation within high-risk prostate cancer are also needed as this may minimise the risk of a high-dose region with less effect on more moderate dose in patients with whole pelvis RT. These results continue to reinforce that rectal hydrogel spacer did not merely delay inevitable declines in bowel function, but rather preserved patient-reported QOL.

Conclusions

Rectal hydrogel spacer effectively preserves overall patient-reported bowel function in men undergoing RT to the prostate alone with long-term follow-up of >24 months. There were fewer declines, both statistically and clinically meaningful, in QOL when hydrogel spacer was used. Specifically, patients with rectal hydrogel spacer placement had less functional decline, and bother of bowel frequency and loose stools at late follow-up.

Conflicts of Interest

Zachary A. Seymour, MD – Augmenix has provided grant for dosimetric analysis unrelated to this publication. Daniel A. Hamstra, MD, PhD – grant and personal fees outside the current study from Augmenix and consultation outside the current study from Boston Scientific. Stephanie Daignault-Newton, MS as consultant for Augmenix. Walter Bosch, DSc, Jeffery Michalski, MD, MBA, Hiram A. Gay, MD – none. Michael Pinkawa, MD, PhD – non-financial support and personal fees from Augmenix outside the submitted work.

References

1 **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: 1250–61

2 **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: 976–85

3 **Pinkawa M**, **Berneking V**, **Schlenter M**, **Krenkel B**, **Eble MJ**. Quality of life after radiation therapy for prostate cancer with a hydrogel spacer: 5-year results. *Int J Radiat Oncol Biol Phys* 2017; 99: 374–7

4 **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: 971–7

5 **Skolarus TA**, **Dunn RL**, **Sanda MG et al**. Minimally important difference for the expanded prostate cancer index composite short form. *Urology* 2015; 85: 101–5

6 **Fischer-Valuck BW**, **Chundury A**, **Gay H**, **Bosch W**, **Michalski J**. Hydrogel spacer distribution within the perirectal space in patients undergoing radiotherapy for prostate cancer: impact of spacer symmetry on rectal dose reduction and the clinical consequences of hydrogel infiltration into the rectal wall. *Pract Radiat Oncol* 2017; 7: 195–202

7 **Quinn TJ**, **Daignault-Newton S**, **Bosch W et al**. Who benefits from a prostate rectal spacer? Secondary analysis of a phase III trial. *Pract Radiat Oncol* 2020 [Epub ahead of print]. DOI: 10.1016/j.prro.2019.12.011.

Correspondence: Zachary A. Seymour, Department of Radiation Oncology, Beaumont Health, Dearborn, MI, USA.

e-mail: zachary.seymour@beaumont.org