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Hydrogel rectum spacer

Who will benefit most from hydrogel rectum spacer implantation in prostate cancer radiotherapy? A model-based approach for patient selection

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ABSTRACT

Background and purpose: Previous studies confirmed that implantable rectum spacers (IRS) decreased acute gastro-intestinal (GI) toxicity in a significant percentage of prostate cancer patients undergoing intensity modulated radiation therapy (IMRT). We developed decision rules based on clinical risk factors (CRFs) to select those patients who are expected to benefit most from IRS implantation.

Materials and methods: For 26 patients dose distributions with (IMRT + IRS) and without (IMRT – IRS) IRS were calculated. Validated nomograms based on CRFs and dosimetric criteria (anorectal V_{40Gy} and V_{75Gy}) were used to predict probabilities for grade 2–3 (G2–3) acute GI toxicity, G2–3 late rectal bleeding (LRB), G3 LRB, and G2–3 faecal incontinence (FI) for IMRT + IRS and IMRT – IRS. All permutations of CRFs were generated to identify most benefit scenarios (MBS) in which a predicted toxicity reduction of $\geqslant$5% points in $\geqslant$25% of the cohort was present due to IRS implantation.

Results: IMRT + IRS revealed a significant reduction in V_{40Gy} ($p = 0.0357$) and V_{75Gy} ($p < 0.0001$) relative to IMRT – IRS. For G2-3 acute GI toxicity and G2–3 LRB, the predicted toxicity rates decreased in 17/26 (65%) and 20/26 (77%) patients, and decision rules were derived for 22/32 (69%) and 12/64 (19%) MBS, respectively. From the decision rules, it follows that diabetes status has no impact on G2–3 acute toxicity, and in absence of pre-RT abdominal surgery, the implantation of an IRS is predicted to show no clinically relevant benefit for G2–3 LRB.

Conclusions: Prostate cancer patients who are expected to benefit most from IRS implantation can be identified prior to IMRT based on their CRFs profile.

Despite recent improvements, image-guided radiotherapy and highly-conformal dose delivery techniques for prostate cancer are still associated with severe gastro-intestinal (GI) toxicity. As a result, a significant percentage of patients suffer from a negative impact on their quality of life [1–3]. Various temporary or long-term implantable medical devices have been developed to spare rectal structures by excluding them from high-dose radiation exposure. Endo-rectal balloons are used to increase the distance from the dorsal rectal wall to the prostate [4]. Implanted rectum spacers (IRS) are used to separate the anterior rectal wall from the prostate by injecting an absorbable hydrogel or hyaluronic acid, or by placing a saline-filled balloon or collagen implant [5–8].

Several studies have confirmed that an IRS decreases the rectal dose and consequently also the acute rectal toxicity to such an extent that the costs of IRS placement are justified [5–14]. A better selection of patients with a decision support system to implant an IRS would further enhance cost-effectiveness, an issue that is becoming increasingly important due to ever-expanding expenses in health care [14,15]. Since the follow-up interval of the studies conducted is still too short, no long-term late toxicity scores have been reported yet. Instead, validated multifactorial nomograms based on clinical risk factors and dosimetric data can be exploited to predict toxicity scores [16,17].

In the current study, we used such nomograms to test the hypothesis that implanting a hydrogel IRS in patients with prostate

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cancer undergoing intensity modulated radiation therapy (IMRT + IRS) reduces the predicted grade 2–3 (G2–3) acute and late rectal toxicities in comparison to patients undergoing IMRT without IRS (IMRT – IRS). Furthermore, we identified scenarios of clinical risk factors for which implantation of an IRS is predicted to significantly reduce G2–3 acute and late rectal toxicity rates in a sufficiently large proportion of patients. Finally, we generate decision rules for the toxicity end-points covering these sets of scenarios, making it possible to select those patients who are expected to benefit most from an IRS implantation prior to treatment planning for IMRT.

Materials and methods

Patient characteristics

This study included 26 patients with localized prostate cancer who had signed an informed consent form, after approval by the ethics committee of the University Hospital RWTH Aachen, where these patients were treated. Patients for this study were consecutively selected in 2011 [5,18]. The patient and tumour characteristics are summarized in Table 1. Prognostic risk-group stratification of the patients was defined according to the D'Amico classification [19].

Table 1
Patient ($N = 26$) and tumour characteristics.

Age (years; median [range])	73 [56–82]
Prognostic risk group[a]: (No. of patients)	
1. Low-risk	8 (31%)
2. Intermediate-risk	11 (42%)
3. High-risk	7 (27%)
Prostate volume: (cm^3; median [range])	
PTV	50 [25–130]
Clinical risk factors for nomograms: (No. of patients)	
Diabetes	4
Haemorrhoids	2
Previous abdominal surgery	2
Anticoagulant drugs	7
Hormonal therapy	7
Anti-hypertensives	11

Abbreviation: PTV = planning target volume.
[a] *Low-risk*: no risk factors: PSA < 10 ng/ml; Gleason score < 7; cT-stage < 2b; *Intermediate-risk:* one risk factor: PSA 10–20 ng/ml or Gleason score = 7 or cT-stage = 2b/c; *High-risk:* two risk factors or PSA > 20 ng/ml or Gleason score > 7 or cT-stage > 2b/c.

Rectum spacer implantation

In these patients, a 10 cm^3 IRS gel (SpaceOAR™ System, Augmenix Inc., Waltham, MA) was injected in the recto-prostatic space prior to IMRT planning and dose delivery. This IRS implantation technique has been described previously by Pinkawa et al. [5].

Image acquisition and organ delineation

Every patient underwent two computed tomography (CT) scans in supine position with a slice thickness of 5 mm: one CT scan prior to IRS implantation and one 3–5 days after IRS implantation. In total, 52 CT scans were imported into the Pinnacle^3 radiation treatment planning system (Version 8.0 m, Philips Medical Systems, Fitchburg, WI) to calculate clinically acceptable dose distributions for IMRT – IRS and IMRT + IRS (Fig. 1). For accurate target volume delineation, T2-weighted magnetic resonance imaging (MRI) scans were additionally performed after IRS implantation. After registration with the corresponding CT scans the prostate, the adjacent rectal wall, and the IRS gel (for volumetric analysis) were contoured.

Depending on the prognostic risk group, the clinical target volume (CTV) was defined as the prostate only (CTV1), the prostate including the proximal 2–4 slices of the seminal vesicles depicted on CT (CTV2), or the prostate with the entire seminal vesicles (CTV3) [20]. To generate the planning target volume (PTV), the CTV was expanded by 8 mm in lateral–anterior, 5 mm in superior–inferior and 4 mm in posterior direction, as described in an earlier study [5,12]. Moreover, the bladder, femoral heads, anus, rectum and the outer anorectal wall contour (anal canal up to the recto-sigmoid flexure) were contoured as organs at risk on the CT scans. To allow for intercomparison between IMRT – IRS and IMRT + IRS planned dose distributions, the delineated craniocaudal distance was chosen to be identical for each patient and for every pre- and post- IRS-implant CT scan, resulting in the same anal and rectal length per patient. Two independent observers (MP and BV) performed the delineations.

Treatment planning technique

All IMRT – IRS and IMRT + IRS treatment plans were designed by inverse planning using a direct machine parameter optimization (DMPO) algorithm for step-and-shoot IMRT with 5 coplanar 15 MV photon beams (gantry angles: 45°, 105°, 180°, 255°, 315°)

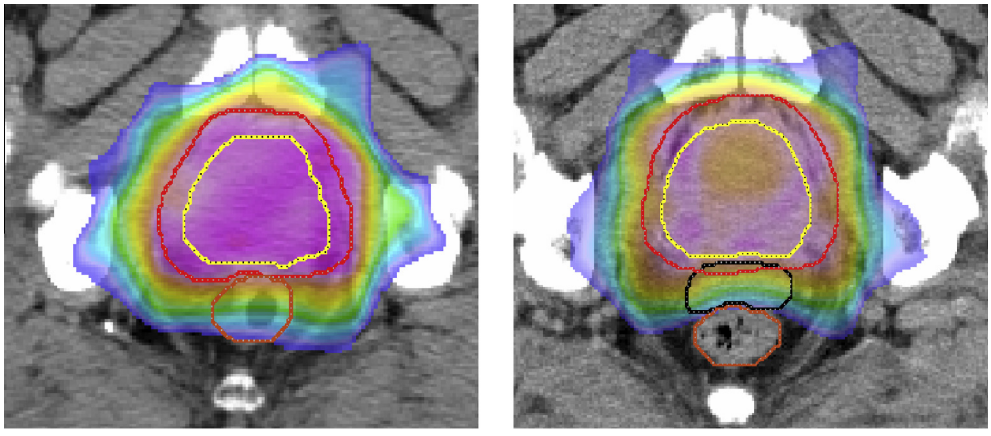

Fig. 1. Color-wash dose distribution in an axial plane before (a) and after (b) IRS gel injection in the same patient, with prostate (yellow) and PTV (red). Without IRS, the high-dose region > 75% (red) overlaps with the anterior part of the rectum (brown), while with IRS *in situ* the high-dose region spans the IRS (black), and not the rectum. The 40% isodose contour (purple) overlaps the entire rectum in (a), whereas it overlaps the rectum partially in (b). *Abbreviation*: IRS = implantable rectum spacer.

[21]. The dose grid included the PTV, organs at risk, and an additional 4–5 cm of tissue in both the cranial and caudal directions. The prescribed dose to the PTV was 78 Gy in 2 Gy fractions, requiring at least 99% of the volume to receive 95% of the prescribed dose within the −5% to +7% ICRU uniformity criteria [22]. The same dosimetric constraints were used for both IMRT − IRS and IMRT + IRS treatment planning, based on the relevant maximum tolerance doses (indicated as D_{max}) and the maximum allowed relative volumes to be exposed to a certain dose level (indicated as V_{xxGy}), as published by the Radiation Therapy Oncology Group (RTOG) for rectum and bladder [23]: V_{50Gy}(rectum) ⩽ 50%, V_{70Gy}(rectum) ⩽ 20%, D_{max}(rectum) ⩽ 76 Gy, V_{55Gy}(bladder) ⩽ 50%, and V_{70Gy}(bladder) ⩽ 30%. The mean anorectal dose (MARD), mean anal dose (MAD), and mean rectal dose (MRD) were evaluated for statistical analysis.

Multifactorial nomograms for NTCP prediction

Validated nomograms based on clinical risk factors (use of anticoagulants, hormonal therapy, or anti-hypertensives; pelvic node irradiation; presence of diabetes or haemorrhoids; and a history of pre-RT abdominal surgery) and dosimetric parameters of the anorectum (V_{40Gy} and V_{75Gy}) were used to predict for each *individual* patient the normal tissue complication probability (NTCP) for G2–3 acute GI toxicity, G2–3 late rectal bleeding (LRB), G3 LRB, and G2–3 faecal incontinence (FI) for both the IMRT − IRS and IMRT + IRS treatment plans [16,17].

Identification of beneficent scenarios

To identify scenarios of clinical risk factors predicting a significant reduction in GI toxicity scores for a sufficiently large proportion of patients, we first considered the most favourable and the most unfavourable scenarios, being defined as the binary permutation of clinical risk factors producing the most positive and the most negative predicted NTCPs, respectively. From the regression coefficients of the nomograms it appeared that 'use of anticoagulants' and 'hormonal therapy' positively affected the predicted NTCPs. On the other hand 'presence of diabetes', 'presence of haemorrhoids', 'pelvic node irradiation', and 'previous abdominal surgery' negatively affected the predicted NTCPs. Consequently, the most unfavourable scenario represents the combination of 'presence of diabetes', 'presence of haemorrhoids', 'pelvic node irradiation', and 'previous abdominal surgery' in absence of 'use of anticoagulants' and 'hormonal therapy'. The most favourable scenario represents the combination of 'use of anticoagulants' and 'hormonal therapy' in absence of 'presence of diabetes', 'presence of haemorrhoids', 'pelvic node irradiation', and 'previous abdominal surgery'. To assess the decrease in predicted NTCPs between IMRT + IRS and IMRT − IRS for both scenarios, the corresponding permutations of risk factors were applied to all individual patients in the cohort, while leaving the variation in dosimetric risk factors unchanged. From the resulting distribution of predicted changes in NTCPs, the proportion having an NTCP reduction of at least 5% and 10% points was assessed for both scenarios. Furthermore, we considered all possible scenarios by generating the remaining binary permutations of clinical risk factors (in total: 32 for G2–3 acute toxicity, 64 for G2–3 LRB, Gr3 LRB, and G2–3 FI) to identify the set of scenarios yielding a predicted NTCP reduction of at least 5% points in at least 25% of the patients. Finally, a Boolean expression[2] for this set of scenarios was generated to establish a decision rule per toxicity end-point.

[2] Propositional formula constructed from simple binary propositions using connectives such as NOT, AND, OR.

Statistical analysis

The statistical analyses were performed using the Statistics and Machine Learning Toolbox™ from MATLAB-software (Version 10.0, MathWorks, Inc., Natick, MA). The Wilcoxon's signed rank test was applied to test for a significant decrease in predicted toxicity rates between IMRT + IRS and IMRT − IRS. All statistical tests were one-sided, with $p < 0.05$ considered to be statistically significant.

Results

Dosimetric plan performance with and without IRS

The median implanted IRS volume was 10.6 cc [range: 8.3–20.4 cc]. No statistically significant difference was observed between the prostate (CTV) and the PTV volumes in IMRT + IRS and IMRT − IRS ($p = 0.269$ and $p = 0.603$, respectively). The median anorectum V_{40Gy} was reduced from 53.4% for IMRT − IRS to 47.6% for IMRT + IRS ($p = 0.0357$). The median V_{75Gy} was significantly reduced from 3.9% for IMRT − IRS to 0.4% for IMRT + IRS ($p < 0.0001$). The median MARD for IMRT − IRS and IMRT + IRS was 38.7 Gy and 34.9 Gy, respectively, yielding a significant reduction ($p < 0.001$). A significant reduction in the median MAD from 34.3 Gy for IMRT − IRS to 24.8 Gy for IMRT + IRS ($p < 0.001$) was observed. The median MRD was significantly reduced from 39.0 Gy for IMRT − IRS to 35.5 Gy for IMRT + IRS ($p = 0.009$).

Predicted NTCP reduction

First, NTCP estimates were calculated for IMRT + IRS and IMRT − IRS based on the clinical risk factors as given for the individual patients. The pair-wise comparison of predicted NTCPs revealed significantly lower predicted G2–3 acute and late rectal toxicity rates for IMRT + IRS than for IMRT − IRS; the decrease was not significant for FI (Table 2). For G2–3 acute toxicity and for G3 LRB, a decrease in predicted toxicity for both endpoints was present in 17/26 (65%) patients. For G2–3 LRB, a decrease in predicted NTCP was expected in 20/26 (77%) patients. For 23/26 patients (88%) no decrease in G2–3 FI was revealed.

In Table 3, the statistics of the predicted NTCPs for both the most unfavourable and most favourable scenarios are presented. For the most unfavourable scenario, the G2–3 acute toxicity rate decreased in 17/26 (65%) patients. For G2–3 LRB, G3 LRB, and G2–3 FI a decrease in predicted toxicity was present in 22/26 (85%) patients, 21/26 (81%) patients, and in 13/26 (50%) patients, respectively. For the most favourable scenario, the G2–3 acute toxicity rate decreased in 17/26 (65%) patients. For G2–3 LRB, G3 LRB, and G2–3 FI a decrease in predicted toxicity was present in 17/26 (65%) patients, 13/26 (50%) patients, and in 1/26 (4%) patients, respectively.

Decision rules

Regarding G2–3 acute toxicity, in 22/32 (69%) scenarios an NTCP-decrease of at least 5% points was predicted to occur in at least 25% of the patients (Table S1, Supplementary Data). The Boolean decision rule that describes these 22 scenarios was found to be:

NOT (A OR E) OR (C AND D) OR (A XOR E) AND (C XOR D)

where A = use of anticoagulants; B = diabetes; C = presence of haemorrhoids; D = pelvic node irradiation; E = hormonal therapy, F = previous abdominal surgery.

Among these 22 scenarios, the most unfavourable scenario and 5/31 additional scenarios had a median NTCP-reduction of at least 5%.

Table 2
Median [range] predicted acute and late toxicity rates in the entire cohort ($N = 26$).

	$NTCP_{IMRT+IRS}$ (%)	$NTCP_{IMRT-IRS}$ (%)	ΔNTCP (%)	*p* value
Nomacu	20 [8–33]	22 [11–32]	3 [−3 to 15]	<0.001
3 yr G2–3 LRB	5 [4–11]	6 [4–13]	1 [−1 to 5]	<0.0001
3 yr G3 LRB	3 [3–10]	4 [4–11]	1 [−1 to 2]	<0.002
G2–3 LFI	1 [0–5]	2 [0–6]	$1^{n.s.}$ [0–2]	$0.006^{n.s.}$

Abbreviations: Nomacu = acute RTOG Grade 2 to Grade 3 lower gastro-intestinal toxicity; 3 yr G2–3 LRB = 3 years of Grade 2 to Grade 3 late rectal bleeding; 3 yr G3 LRB = 3 years of Grade 3 late rectal bleeding; G2–3 LFI = chronic Grade 2 to Grade 3 late faecal incontinence; IRS = implantable rectum spacer. $^{n.s.}$Not significant.

Table 3
Median [range] predicted acute and late toxicity rates stratified by scenario.

	Scenario	$NTCP_{IMRT+IRS}$ (%)	$NTCP_{IMRT-IRS}$ (%)	ΔNTCP (%)	*p* value	ΔNTCP ⩾ 5% (%)	ΔNTCP ⩾ 10% (%)
Nomacu	MU	45 [33–54]	48 [39–59]	5 [−4 to 20]	<0.001	50	12
	MF	10 [6–14]	11 [8–16]	2 [−2 to 8]	<0.001	4	0
3yr G2–3 LRB	MU	17 [13–21]	22 [15–30]	5 [−4 to 16]	<0.0001	50	12
	MF	4 [3–4]	5 [4–6]	1 [−1 to 3]	<0.0001	0	0
3yr G3 LRB	MU	13 [11–16]	17 [12–22]	3 [−2 to 10]	<0.0001	19	0
	MF	3 [2–3]	3 [3–4]	1 [0–2]	0.02	0	0
G2–3 LFI	MU	12 [7–17]	13 [9–19]	1 [−3 to 12]	0.03	12	4
	MF	0 [0–1]	1 [0–1]	0 [0–1]	$0.06^{n.s.}$	0	0

Abbreviations: MU = most unfavourable scenario; MF = most favourable scenario; $NTCP_{IMRT+IRS}$ = normal-tissue complication probability for IMRT plans with IRS gel; $NTCP_{IMRT-IRS}$ = normal-tissue complication probability for IMRT plans without IRS gel; ΔNTCP ⩾ *x*% = percentage of patients in study cohort having an NTCP decrease of at least *x*% points; IRS = implantable rectal spacer; Nomacu = acute RTOG Grade 2 to Grade 3 lower gastro-intestinal toxicity; 3 yr G2–3 LRB = 3 years of Grade 2 to Grade 3 late rectal bleeding; 3 yr G3 LRB = 3 years of Grade 3 late rectal bleeding; G2–3 LFI = chronic Grade 2 to Grade 3 late faecal incontinence; IRS = implantable rectum spacer. $^{n.s.}$Not significant.

For G2–3 LRB, in 12/64 (19%) scenarios an NTCP-decrease of at least 5% points was predicted to occur in at least 25% of the patients (Table S2, Supplementary Data). The Boolean decision rule that describes these 12 scenarios was found to be:

$$F \text{ AND } (\text{NOT } (A) \text{ AND } ((B \text{ OR } C) \text{ AND } (D \text{ AND } E) \text{ OR NOT } (D \text{ OR } E))) \text{ OR } (\text{NOT } (C) \text{ AND } D \text{ AND NOT } (E)) \text{ OR } (C \text{ AND } D \text{ AND NOT } (E))$$

where A = use of anticoagulants; B = diabetes; C = presence of haemorrhoids; D = pelvic node irradiation; E = hormonal therapy, F = previous abdominal surgery.

For G3 LRB and G2–3 FI an NTCP-decrease of at least 5% points was not predicted to occur in at least 25% of the patients.

Discussion

This is the first study to assess the benefits of an IRS for reducing GI toxicity in prostate cancer patients scheduled for IMRT prior to implantation of such a device. We identified combinations of clinical risk factors for which IRS implantation is predicted to be beneficial. For two clinically relevant toxicity end-points, we generated decision rules to identify patients who are expected to benefit most from the implantation of an IRS, based solely on their clinical risk profiles and not on dosimetric or genetic factors. The probability of developing GI toxicity is not only related to the dose and the volume of the anorectum receiving a high radiation dose, but also depends on clinical risk factors and genetic profiles. GI toxicity is a concern in EBRT of prostate cancer and its adverse effect on the quality of life cannot be ignored. Dose-escalated IMRT up to a dose of 78 Gy has raised the rates of acute and chronic Grade ⩾ 2 rectal toxicity compared with lower doses (e.g., 68 Gy) from 3% to 20% and 5% to 21%, respectively [24–28]. Keeping the volume fraction of the anorectum receiving more than 75 Gy (V_{75Gy}) below 5% has been demonstrated to be predictive of late rectal bleeding [29]. Therefore, it is important to use techniques that prevent rectal volumes from being exposed to high doses. Implantation of an absorbable IRS between the prostate and the anterior rectal wall artificially increases the distance between the prostate and the anterior rectal wall, and hence reduces the dose delivered to the anorectum [30,31]. Besides dosimetric factors, several clinical risk factors have been shown to predict for radiation-induced GI toxicity in prostate cancer patients. Based on combinations of scenarios of clinical risk factors, we developed the first set of decision rules to predict the estimated toxicity reduction of an IRS prior to implantation. This introduces the opportunity to better select patients for IRS implantation, avoid unbeneficial implantations and possible complications, enhance quality of life, and consequently improve the cost-effectiveness of the treatment. In addition to dosimetric and clinical factors, the prediction could possibly be further improved by including genetic biomarkers to select those patients having increased risk factors for increased rectal toxicity [32–34]. Recently the first replicated genetic associations were reported for adverse reactions to EBRT [35]. A next step could therefore be to incorporate genetic risk in those models [34].

The multifactorial nomograms by Valdagni et al. were used in our study to predict acute and late toxicity rates [16,17]. In our patient group, these nomograms revealed a significant decrease in G2–3 acute and late GI toxicity. When we compared the most unfavourable with the most favourable scenario, a most unfavourable scenario was predicted to be beneficial with IMRT + IRS, while the benefit in the most favourable scenario was minimal. Between those two extreme scenarios, multiple other scenarios were identified yielding a predicted NTCP reduction of at least 5% points in at least 25% of patients. To select patients for IRS implantation, the concept of late rectal toxicity as a consequential late effect arising from acute RT injury is important [36]. This implies that the decision rule we developed to predict a clinically relevant reduction of acute toxicity in a sufficiently large proportion of patients after implantation of an IRS, could be used to select optimal candidates for implantation of an IRS, and hence reduce acute and consequently late toxicities. Regarding G2–3 acute toxicity, in 22 scenarios an NTCP-decrease of at least 5% points was predicted to occur in at least 25% of the patients (Table S1). The interpretation of the corresponding decision rule covering these scenarios is as follows: first, the conjunction of absence of 'use of anticoagulants' and absence of 'hormonal therapy' represents 8 scenarios that correspond to the Boolean expression NOT (A OR E) (Table S1). Secondly,

6 additional scenarios are provided by the conjunction of both 'presence of haemorrhoids' and 'pelvic node irradiation'. This corresponds to the Boolean expression (*C* AND *D*). The remaining 8 scenarios are described by the presence of either 'use of anticoagulants' or 'hormonal therapy', in conjunction with either 'presence of haemorrhoids' or 'pelvic node irradiation'. This corresponds to (*A* XOR *E*) AND (*C* XOR *D*). These 3 expressions are combined in a disjunctive way to establish the full decision rule. From this decision rule, it follows that diabetes status has no impact on the decision rule. For G2–3 LRB, in 12 scenarios an NTCP-decrease of at least 5% points was predicted to occur in at least 25% of the patients. From the corresponding rule, it follows that in absence of pre-RT abdominal surgery, the implantation of an IRS is predicted to show no clinically relevant benefit for G2–3 LRB.

The present study has several limitations. First, the confidence intervals of the regression coefficients in the logistic regression model of the nomograms were not incorporated in our analysis. Hence, confidence intervals for the predicted NTCPs have not been computed, possibly leading to an over- or underestimation. Furthermore, the nomograms used were gathered from clinical data acquired between 2002 and 2004, an era of less conformal dose delivery techniques compared to modern IMRT. Nowadays, IMRT with daily image-guided set-up correction enables accurate dose delivery, thus possibly enhancing the non-dosimetric predictors of rectal toxicity. Moreover, the two decision rules we developed are based on different clinical risk factors, and not on dosimetric factors. Further, the nomograms used are only internally validated, and stand in need of external clinical prospective validation. Next, as far as the predictive performance of the decision rules is concerned, their sensitivity, specificity, and calibration have to be assessed in an independent test-population. Finally, other prediction models exist with other clinical factors that might influence acute and late GI toxicity [37,38]. Hamstra et al. reported that patient age, a history of myocardial infarction, and congestive heart failure are predictors for G3 GI toxicity [37]. However, they concluded that the use of anticoagulants increased toxicity independent of age and comorbidity. The use of anticoagulants is already included in the nomograms of Valdagni et al. Tucker et al. also reported that patients with cardiovascular disease had a significantly higher incidence of late rectal toxicity [38]. Those risk factors have not been included in the nomogram of Valdagni et al. This is therefore a limitation of their prediction model.

In the present study, we evaluated differences in predicted NTCP due to the implantation of an absorbable hydrogel spacer. We investigated combinations of clinical risk factors to generate decision rules in order to predict clinical scenarios in which patients are expected to benefit most from spacer implantation. Wolf et al. recently published a study comparing the dosimetric differences between various spacing methods, showing that balloon spacers had a more pronounced effects than hydrogel spacers [39]. At the time of planning, balloon spacers revealed a 63% reduction of the rectum surface encompassed by the 95% isodose-line, in comparison to 38% for the hydrogel. However, they were unable to demonstrate any clinically relevant difference in acute GI toxicity. The relevant scenarios of clinical risk factors that were identified in our study are based on treatment plans with and without an implanted hydrogel. Our method could also be applied to patients with an implanted balloon spacer. According to the nomograms, balloon spacers would probably not decrease acute toxicity more than hydrogel spacers, because of similar mean rectal dose. However late toxicity is expected to decrease with balloon spacers due to a lower V_{75Gy} in comparison to hydrogel spacers. Further research is needed to test this hypothesis.

The results presented in this paper are also valuable for policy making by health care insurance companies. Currently, there is no reimbursement for IRS implantation in the Netherlands. Only new treatment modalities with level I–II scientific evidence are approved for reimbursement. A reliable patient-selection tool may fundamentally change this procedure. A model-based approach could possibly be instrumental for this, since such an approach was also employed for the introduction of proton therapy in the Netherlands. According to guidelines of the Dutch National Society of Radiotherapy Oncology, a predicted reduction of 10% of grade 2, 5% of grade 3 and 2% of grade 4–5 complications would be required to justify the increased costs for such treatment [40]. If we apply these thresholds, we estimate that approximately 20% of the localized prostate cancer patients would benefit from an IRS, and consequently should have its placement reimbursed. If the IRS is combined with brachytherapy, proton therapy, or stereotactic radiotherapy, the toxicity reduction may even be more pronounced due to the steep dose gradients of these techniques. However, this hypothesis needs to be clinically validated.

The next step will be to implement the cost-effectiveness model to obtain a four-level decision support system with complete integration of dose, toxicity, cost-effectiveness, and genetic input [41,42].

In conclusion, the implantation of an IRS is predicted to reduce the G2–3 acute and late rectal toxicity rates in prostate cancer patients undergoing IMRT. Scenarios of clinical risk factors were identified for which implantation of an IRS is predicted to significantly reduce G2–3 acute and late rectal toxicity rates with IMRT prior to implantation of the IRS. Decision rules were developed to support the physician in selecting those patients who will benefit most from IRS implantation prior to IMRT planning. A prospective follow-up study in an independent patient cohort is needed to assess the predictive performance of the decision rules.

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Conflict of interest statement

All authors declare to have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2016.08.026.

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