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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°)

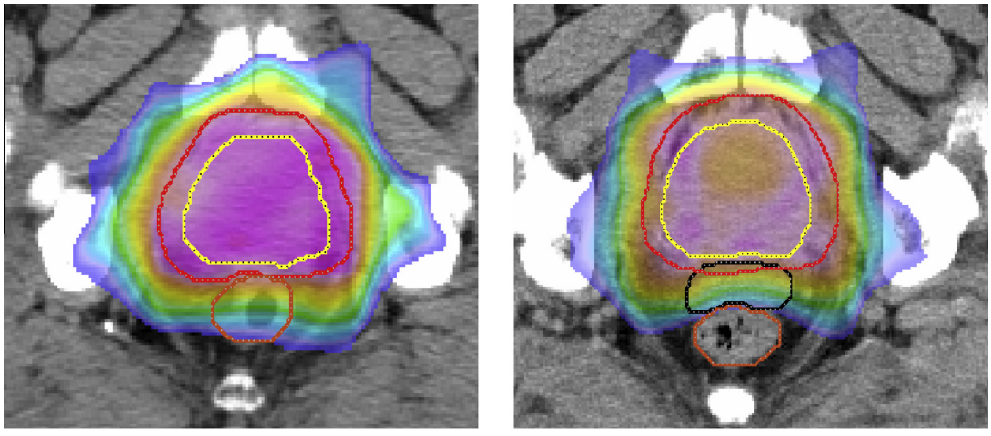

Fig. 1. Color-wash dose distribution in an axial plane before (a) and after (b) IRS gel injection in the same patient, with prostate (yellow) and PTV (red). Without IRS, the high-dose region > 75% (red) overlaps with the anterior part of the rectum (brown), while with IRS *in situ* the high-dose region 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.