Radiotherapy and Oncology 106 (2013) 210–214

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Rectal spacing in prostate RT

Interstitial biodegradable balloon for reduced rectal dose during prostate radiotherapy: Results of a virtual planning investigation based on the pre- and post-implant imaging data of an international multicenter study ☆

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ARTICLE INFO

Article history:
Received 6 December 2011
Received in revised form 27 December 2012
Accepted 27 January 2013
Available online 26 February 2013

Keywords:
Prostate
Rectal dose
Tissue separation
OAR dose reduction

ABSTRACT

Purpose: To evaluate dose reduction caused by the implantation of an interstitial inflatable and biodegradable balloon device aiming to achieve lower rectal doses with virtual 3D conformal external beam radiation treatment.

Materials and methods: An inflatable balloon device was placed, interstitially and under transrectal ultrasound guidance, into the rectal–prostate interspace prior treatment initiation of 26 patients with localized prostate cancer, who elected to be treated with radiotherapy (3D CRT or IMRT). The pre- and post-implant CT imaging data of twenty two patients were collected (44 images) for the purpose of the 3D conformal virtual planning presented herein.

Results: The dorsal prostate–ventral rectal wall separation resulted in an average reduction of the rectal V70% by 55.3% (±16.8%), V80% by 64.0% (±17.7%), V90% by 72.0% (±17.1%), and V100% by 82.3% (±24.1%). In parallel, rectal D2 ml and D0.1 ml were reduced by 15.8% (±11.4%) and 3.9% (±6.4%), respectively.

Conclusions: Insertion of the biodegradable balloon into the prostate–rectum interspace is similar to other published invasive procedures. In this virtual dose distribution analysis, the balloon insertion resulted in a remarkable reduction of rectal volume exposed to high radiation doses. This effect has the potential to keep the rectal dose lower especially when higher than usual prostate dose escalation protocols or hypo-fractionated regimes are used. Further prospective clinical investigations on larger cohorts and more conformal radiation techniques will be necessary to define the clinical advantage of the biodegradable interstitial tissue separation device.

Although radiation therapy has the potential to cure locally confined prostatic tumors in selected patients, it can also result in significant morbidity, potentially leading to lifestyle restrictions and psychological distress. Patient quality of life (QoL) following primary treatment of localized prostate cancer is, to a large extent, influenced by adverse changes in bowel, urinary, and sexual function. While local dose escalation has been shown to significantly improve outcomes of radiotherapy of local and locally advanced prostate cancer [1,2], rectal toxicity [3] limits the extent of acceptable escalation [4]. A number of technical developments aim to reduce rectal radiation dose [5–8], some of which rely on tissue separation between the dorsal prostate and ventral rectal wall [9–13].

A biodegradable and inflatable balloon device (ProSpace®, BioProtect Ltd./Israel) has been designed to be transperineally implanted within the prostate–rectum interspace, before treatment initiation, to increase the gap between the prostate–rectum. The device remains inflated during the entire treatment period and biodegrades in the body some weeks after termination of treatment. In the BPI-01 international, multicenter study (NCT00918229), the device proved to increase the prostate–rectum distance 10-fold (mean 0.22 ± 0.2 cm to 2.47 ± 0.47 cm), and to remain stable during radiotherapy. In parallel, a significant mean reduction in calculated rectal radiation exposure was achieved. The implant procedure was well tolerated and the adverse events included mild pain at the perineal skin and in the anus. Three patients experienced acute urinary retention, which may have been triggered by the use of general anesthesia, and resolved within a few hours of conservative treat-

☆ The paper was partly presented at ESTRO 30 in London as a poster presentation. All authors read and accepted the manuscript before submission.

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http://dx.doi.org/10.1016/j.radonc.2013.01.007

ment. No infections or thromboembolic events occurred during the implant procedure or during radiotherapy [12–14].

As each treatment center in the BPI-01 study used its standard institutional radiation protocols (3DCRT, IMRT), which included different radiation techniques and dosages, the present work provides a centralized, radiation technique-independent analysis of the changes in rectal radiation exposure. A virtual radiation dose model, based on pre- and post-implant CT image series is presented.

Material and methods

In the framework of an international multicenter study (BioProtect, BPI-01), conducted after approval by the local Institutional Review Boards, FDA and the respective Ethics Committees and Ministries of Health, ProSpace (BioProtect Ltd., Israel) was transperineally implanted, under transrectal ultrasound guidance and local/general anesthesia, within 2 weeks of the start of radiotherapy, within the prostate–rectal interspace of 26 patients with histologically confirmed, localized prostate cancer [12–14]. Weekly CT/US scans were performed during EBRT and at 3, 6 and 12 months after balloon implantation, to evaluate stability and subsequent degradation of the balloon. Radiation treatment planning and delivery were executed as per the standard protocols of the participating center. The pre- and post-implant CT images of 22 study patients were collected to virtually determine the dose at the treated region before and after implantation. CT series of 4/22 patients were not eligible for this analysis, due to varying slice thicknesses. The implantation procedure as well the feasibility study results were described elsewhere [12–14]. Radiation treatment planning and delivery were executed as per the standard protocols of the participating center.

Contouring of prostate and rectal wall in both pre- and post-implant images was performed by one physician (GB, experienced in delineation work) and dose calculations were performed by one medical physicist (CM), with identical radiation parameters for all cases. The Planning Target Volume (PTV) was defined in 1.0 cm extensions in all directions margin to the prostate. In post-implant images the balloon was also contoured. After creating these 44 virtual plans, changes in rectal dose–volume-histograms (DVH) were measured and compared to rectal tissue dose values with and without the implanted balloon.

The potential dose reduction on the rectum due to the enlarged distance between prostate and ventral rectal wall, was calculated by determining the differences in V50%, V60%, V80%, V90% and V100% (Vxx% = the volume in % of the rectum wall receiving xx% of the prescribed dose) at the prescribed dose level of 74 Gy. Rectal wall volume data were compared by using D2 ml and D0.1 ml (Dxx ml is defined as the minimum dose in Gy in the most irradiated rectal wall volume of xx ml [15]). Similarly, when calculating affected rectal volume, presentation in percentage form allows for the most effective comparison between all 22 patients. Statistical significance of volume (Vxx%) and dose (Dxx ml) reductions were tested by a single-sided, paired Student's *t*-test. A significance level of 0.01 was chosen.

A four-field box technique was used (18 MeV photons, field at 0°, 90°, 180°, and 270°) in the treatment planning system (TPS) ECLIPSE© (Varian, Paolo Alto, USA). The planning was performed on CT data sets with a slice thickness of 2 mm. The "half-beam technique" was applied and the isocenter was placed close to the rectum in order to achieve lower rectal doses due to the lower weight of the 180° field. The field size multileaf collimators (MLC) were optimally fitted, in each case. The reference dose of 74 Gy (conventional fractionation) was prescribed on the 100% isodose. ICRU recommendations were followed. Preparation of pre- and post-implant radiation plans was performed on the basis of identical procedures: isocenters for both plans were on the same place, D_{max} values were comparable and field lengths were equal since the CTV was not changed.

GEC-ESTRO dose recording and reporting recommendations for prostate brachytherapy were adapted to rectal tissue dose reporting [16].

Results

Typical pre- and post-implant organ geometries are shown in Fig. 1. The mean measured post-implant prostate–rectum distance, on the anterior–posterior axis was 19.15 mm (range 14.6–23.4 mm). The mean latero-lateral extension of the balloon was 30.45 mm (range 21.1–36.6 mm), cranio-caudal 45 mm. The attained median dose reduction in % as well the corresponding standard deviation values (SD) is summarized in Table 1.

In an effort to normalize the different dose regimens applied at the participating centers, changes in dose are presented as the percentage of the total dose. Vxx% represents the rectal wall volume in %, which receives a dose of xx% in Gy of the prescribed dose. Dxx ml is defined as the minimum dose in Gy in the most irradiated rectal wall volume of xx ml [15].

The size of the rectum wall volume included into the radiation field is individually different. Separate CT-data result in a different size (ml) of the affected volume of the rectum wall even for the same patient. A comparison of the volume in absolute value with the unit ml is ineffective. Percent offers the option to become a comparable value to all results of the 22 patients.

The volumes receiving 37 Gy (V50%) showed very small changes on average, and ranged from volume increase of 31% in one patient to a volume decrease of 35% in another patient.

The minimum volume reduction was about 30% and the maximum nearly 100% for all volumes receiving more than 52 Gy (V70%, V80%, V90%, and V100%). The high dose values of a 2 ml volume (D2 ml) decreased by a mean 16% (SD = 11.4%; range: 3–42%). The influence of the balloon implantations was smaller for the very small volumes, and yielded a mean 4% (±6.4%; range: −1–27%) for D0.1 ml. With the exception of V50%, all volume reductions were significant. The same significance holds for the dose reduction of D2 ml and D0.1 ml.

The observed SD of ±20% seems to be relatively high – the explanation for that is apparently that the pre-implant and postimplant CT data showed differences in rectal shape and volumes in the same patient.

The reduction in rectal dose upon use of the ProSpace© balloon is highlighted when comparing the pre-implant and post-implant rectal DVHs. Corresponding anterior-posterior dose profiles are shown in the lower part of Fig. 1. The marked region indicates transposition of rectal wall volume from an area of steep dose gradients (Fig. 1, down left) into an area of lower dose plateau regions (Fig. 1 down right). Relevant influences on DVHs are presented in Fig. 2, where both pre-implant and post-implant rectal DVHs are co-plotted. A strong rectal dose fall-off expresses itself in 39–42 Gy range of the DVH, namely, at 50–60% of the prescribed dose. The DVHs also demonstrate that a much smaller rectal volume will be exposed to >42 Gy in the post-implant versus the pre-implant setup. Furthermore, DVHs show that the post-implant rectal wall volume receiving <39 Gy increases. A very small fraction of rectal volumes (2.0 and 0.1 ml) is exposed to the highest dose values.

Discussion

The use of an interstitial spacer is intended to reduce rectal dose and toxicity, where the benefit of enlarged prostate–rectum spaces

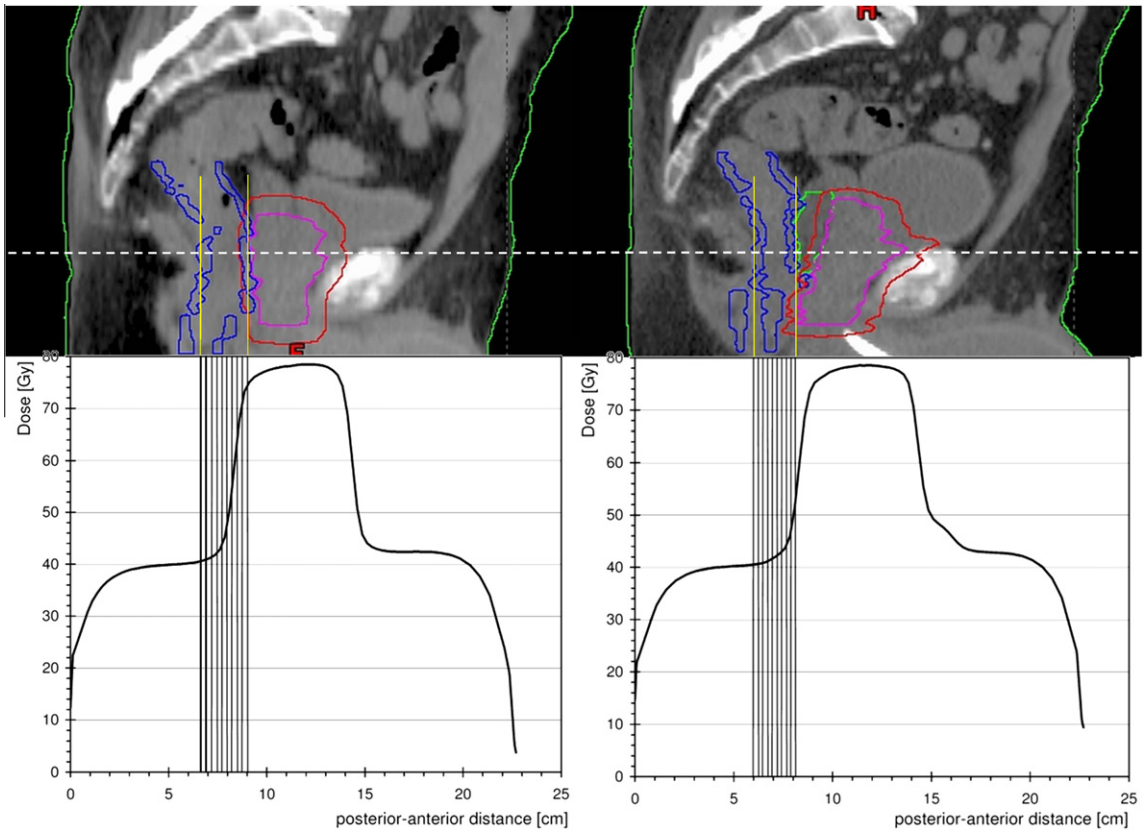

Fig. 1. A comparison is shown between an irradiation plan on sagittal reconstructed images together with a dose profile in posterior–anterior direction along the white dashed line prior to balloon implantation (left side) and a plan on CT-images of the same patient with balloon implanted (right side), here the separation between rectum (blue) and prostate (magenta) can be clearly seen; PTV (red), prostate (magenta), and body outline (green). In the lower part the hatched area clarifies the shift of the rectum wall to the lower dose plateau due to the balloon implantation.

Table 1
Changes in Δ_{mean} of dose and their SD values for rectal dose of all 22 patients in the preimplant as well postimplant situation. Vxx% = the volume in % of the rectum receiving xx% of the prescribed dose, and Dxx ml is defined as the minimum dose in Gy in the most irradiated rectal wall volume of xx ml [20]. Negative values of V50% mean higher rectal volumes receiving 50% of the prescription dose after balloon implantation.

	V50%	V70%	V80%	V90%	V100%	D2 ml	D0.1 ml
Δ_{mean}	−0.3	55.3	64.0	72.0	82.3	15.8	3.9
SD	13.5	16.8	17.7	17.1	24.1	11.4	6.4

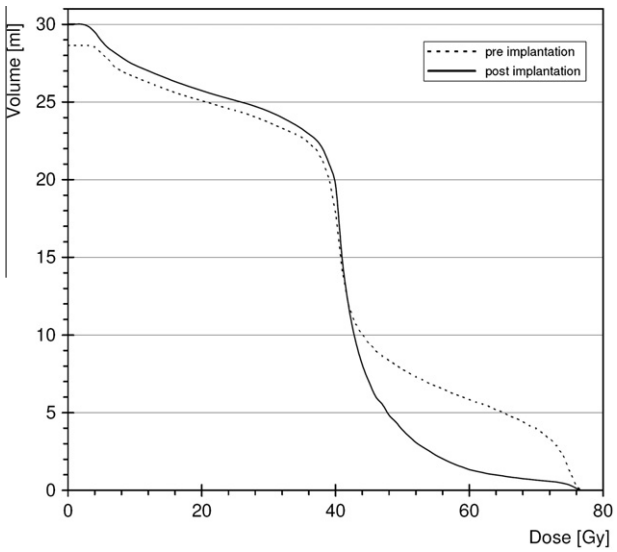

Fig. 2. Dose–volume-histograms (DVH) of the rectum; without (dotted line) and with balloon (solid line). The reduction of volume with a high dosage can clearly be seen.

increases with treatment intensity by additional dose escalation, especially in hypofractionation. However, when increasing the radiation dose to all or part of the prostate, normal tissue toxicities could become limiting factors [10,17]. High radiation dose (above 70 Gy) reaching the rectum during dose escalated treatments is a predictor for late rectal toxicity [3]. One of the published methods aiming to enlarge the prostate–rectum interspace is the biodegradable and inflatable interstitial balloon (ProSpace®, BioProtect Ltd., Israel) which was investigated in the BPI-001 study. Results of this pilot study of 26 patients showed that the balloon insertion process is safe and the implantation procedure has a quick learning curve. The balloon remained in its inflation location throughout its life time, remained inflated throughout the standard period of radiation therapy and there were no procedure/balloon related unexpected adverse events. A satisfactory separation was achieved and remained at least 1 cm throughout the radiation treatment period and averaged more than 1.5 cm. All implanted balloons started to degrade as expected after 3 months post implantation [14]. Since radiation techniques and protocols were on discretion of the participating study centers and contouring is a strongly observer and imaging method dependent procedure [18], all pre- and post-implantation cross sectional imaging data of the BPI-01 study were collected in one center and both contouring workload as well virtual radiotherapy treatment planning were

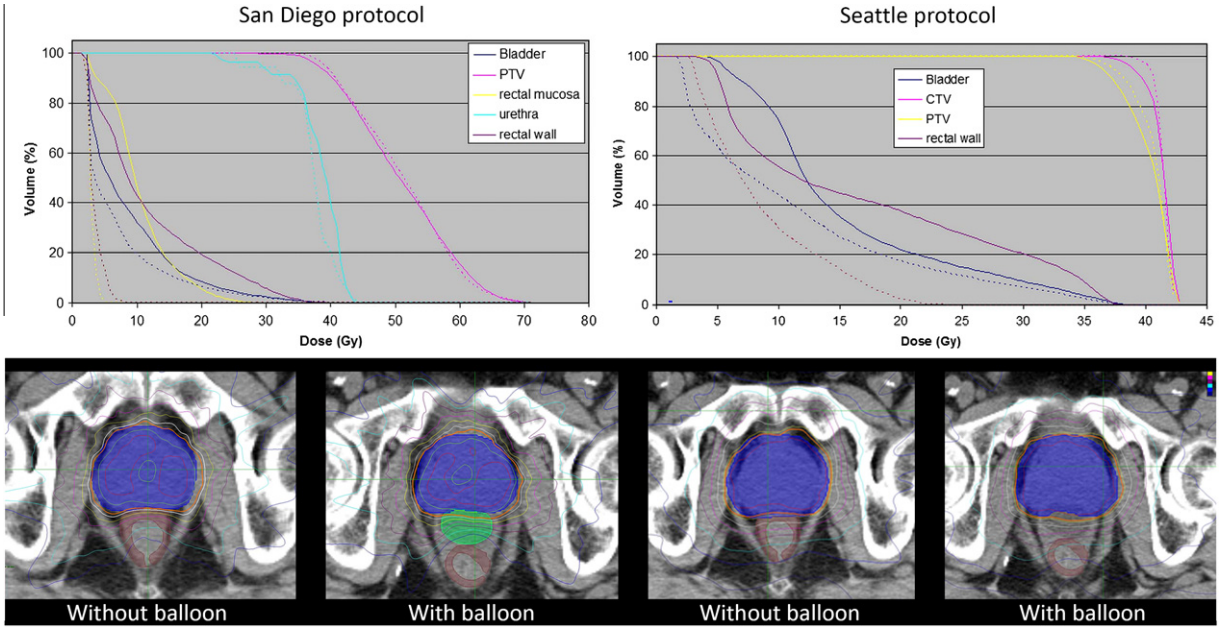

Fig. 3. The effect of balloon implantation on dose distribution in the case of virtual planning for the Cyber Knife system is shown together with the dose–volume histograms (DVH) for two protocols: on the left side virtual planning according to the San Diego protocol (inhomogeneous dose distribution) and on the right side according to the Seattle protocol (homogeneous dose distribution). Solid lines in the DVHs for irradiation without a balloon, and dotted lines for irradiation after balloon implantation.

Table 2
Literature based comparison of the PEG-hydrogel and ProSpace® devices.

	Balloon system	PEG-Hydrogel [10,17]
Implantation	Variable	Variable
Spacer shape	Constant after inflating	Unpredictable
Degradation starts	Min. 13 weeks	4–8 weeks
Compliance	Non-compliant	Compliant
Geometric stability	Stable	Unstable
Placement correction	Possible	Not possible
Implantation time	Not limited	Need to be short
CT visibility	Excellent	Poor

performed by the same personnel to avoid inter observer variations.

In the four-field approach, the rectal tissue will be "pushed out" from the lateral fields, due to the half beam box technique and the balloon implantation. In the anterior–posterior fields, no changes are expected, so the full radiation dose of these fields will be absorbed by this structure. Therefore, the distance between prostate and dorsal rectal wall is critical in determining the dose received by the rectum. A strong rectal dose reduction is shown by the DVH at the 39–42 Gy range. This high dose gradient is 50–60% of the prescribed dose. It can also be observed on the DVHs that a much smaller rectal volume receives more than 42 Gy in the post-implant compared to the pre-implant values. At V90% (rectal wall volume receiving 66.6 Gy) dose is reduced by 72%. Furthermore, DVHs show that the post-implant rectal volume receiving <39 Gy increases, due to the shift-out of the rectal tissue from the lateral fields, while still remaining in the anterior–posterior fields. The individual patient data presented in Fig. 1 demonstrate that ProSpace© balloon implantation yielded a 24.45% reduction of the 0.2 ml rectal wall volume, from 74.26 Gy total dose to 56.1 Gy. The 0.1 ml rectal wall volume receives 76.39 Gy before the implantation and 76.1 Gy after balloon implantation. This minor reduction is seemingly due to failure of the balloon to push out the complete rectal volume from the field.

The observed SD of ±20% seems to be relatively high – the explanation for that is apparently that the pre-implant and post-implant CT data showed differences in rectal shape and volumes in the same patient.

The relatively "old-fashioned" conformal radiotherapy method (four-field technique with the use of multileaf collimators) used in this study is still widely applied and was chosen because of its easy handling and relatively high rectal dose. Furthermore, this virtual planning investigation focused on the rectal dose changes promoted by the interstitial spacer device. Therefore, unlike the typical clinical routine, we did not include common conformation methods, such as reduction of the margin added to the CTV dorsally from the prostate, planning a boost with reduced margins to CTV or usage of more conformal techniques (IMRT, tomotherapy, etc.). In order to evaluate the benefit of the rectal dose reduction with more conformal radiation techniques, eligible CT series were also used for virtual planning for the Cyber Knife® (Accuray, USA) system. We chose this system, because in our opinion, smaller PTV margins are used for CK planning, when compared to IMRT, and dose gradients are steeper. Although there are several limitations, the dose sparing effect of the balloon implantation provided for a significant rectal wall and mucosa dose reduction, without impacting target coverage or other OAR sparing (Fig. 3). However, the presented analysis is based on a single case-study, and so caution must be exercised when extrapolating to the larger patient population.

Other limitations of the use of the CT images for the CK planning purposes were the scan extent that was inadequate to allow beams from many inferior nodes in the prostate specific path. The full body path was used instead to maximize number of nodes. This should be regarded as worse than what would be possible with a full CT scan. In addition, the pre- and post-implant CT scans were acquired at different times and show different bladder, rectum, and prostate volumes, adding uncertainty to the comparison performed. A virtual plan was generated with both, the San Diego and the Seattle protocols, both of which were hypofractionated regimes. The San Diego protocol is designed to emulate HDR implant type dose distributions, while the Seattle protocol delivers a more uniform dose to the prostate. In both cases, the reduction in rectal dose was much higher than in the "suboptimal" 3DCRT plans and a

remarkable reduction in the rectal maximum dose was also observed (Fig. 3).

Recently, a number of publications have described injection of a blood patch, hyaluronic acid or PEG-hydrogel as a means to heighten the interstitial prostate–rectum separation [9–11,17,19,20]. More specifically, Susil et al. [10] reported reduced rectal radiation doses after injecting PEG-hydrogel into the space between the rectum and prostate. In 2012, Pinkawa et al. [19] investigated the quality of life of patients receiving different kinds of radiotherapy (3DCRT, IMRT) with or without the application of an interstitial spacer. Median dose to the prostate in the spacer subgroup was 78 Gy, conventionally fractionated. The results were independently compared with two matched-pair subgroups (conventionally treated without a spacer): 3D conformal 70.2 Gy in 1.8 Gy fractions and intensity-modulated radiotherapy (IMRT), 76 Gy in 2 Gy fractions. There were 28 patients in each of the three groups. They stated that "Bowel bother scores" were significantly improved in comparison to baseline levels in the spacer cohort only. Percentage of patients reporting moderate/considerable bother with specific symptoms did not increase for any item (urgency, frequency, diarrhea, incontinence, bloody stools and pain).

While the implantation procedure of both the balloon and the hydrogel is similar, differences remain in the handling of the two interstitial spacer materials. The PEG hydrogel does not support any postimplant correction, yet, the inflated balloon can be easily deflated and replaced if mispositioned. In the case of PEG-hydrogel, the user is limited by the short time in which the chemical reaction between the two components takes place. In contrast, the interstitial balloon does not have a limited handling time in the initial implantation step. Although, there is no published comparative investigation in the literature, published CT images with the PEG hydrogel suggest superior CT visibility of the balloon, when compared to the hydrogel, which is most advantageous in treatment planning procedures. A comparison of ProSpace® balloon and PEG hydrogel-based interstitial spacer is summarized in Table 2.

Conclusion

Insertion of the biodegradable balloon into the prostate–rectum resulted in a remarkable reduction of the rectum volume exposed to high radiation doses. This effect has the potential to maintain low rectal radiation exposure when dose escalation protocols are necessary, especially with hypofractionated regimes. Further prospective clinical investigations on a larger number of patients and more conformal radiation techniques will be necessary to define the clinical advantage of the biodegradable interstitial tissue separation device.

Disclosure

Adrian Paz MD is co-founder of the ProSpace® balloon manufacturer, BioProtect.

Rami Ben Yosef MD is a BioProtect advisory board member.

Benjamin W. Corn, MD is a BioProtect advisory board member.

György Kovács MD PhD is a BioProtect advisory board member.

BPI-01 Study (One-arm, multi-center, international prospective study to assess the safety and efficacy of BioProtect biodegradable implantable balloon in prostate cancer subjects undergoing radiotherapy) was sponsored by BioProtect Ltd./Israel.

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