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ORIGINAL PAPER

Safety and tolerability of biodegradable balloon spacers in patients undergoing radiotherapy for organ-confined prostate cancer

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Summary *Introduction: Radiotherapy is a common treatment for prostate cancer, and can be administered in various ways, including 3D conformal radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT) and hypo-fractionated radiation therapy. During treatment the gastrointestinal tract may be exposed to radiation and the rectal wall may be exposed to high doses of ionizing radiation, which can lead to rectal bleeding, ulcers or fistulas, and an increased risk of rectum cancer. Various strategies to minimize these complications have been developed in the last decade; one of the most promising is to use a rectal balloon to fixate the prostate gland during treatment or to inject biodegradable spacers between the prostate and rectum to reduce the rectal dose of radiation. Aim of our paper is to evaluate the safety and tolerability of spacers implantation.*

Materials and methods: From January 2021 to June 2022 all patients with a diagnosis of prostate cancer with unfavorable/intermediate risk - poor prognosis and programmed hypofractionated radiation therapy were enrolled.

In all patients biodegradable balloons spacers were placed posteriorly to the prostate to increase the separation between prostate and rectum. The duration of the procedure, observation time, the appearance of early and late complications and their severity (according to Charlson comorbidity index) and tolerability of the device were recorded at the time of positioning and after 10 days.

Results: 25 patients were enrolled in our study. Two patients (8%) underwent acute urine retention resolved with catheterization and one patient (4%) developed a mild perineal hematoma that did not require any treatment. As regards late complications 1 patient (4%) developed hyperpyrexia (> 38°C) the day after the procedure requiring continuation of antibiotic regimen. At T1 visit we recorded no medium-high grade complications. As for the tolerability of the device, it was optimal with no perineal discomfort or alterations of bowel function.

Conclusions: Biodegradable balloon spacers appears to be safe and well tolerated and its positioning does not present any technical difficulties or risks of major complications.

KEY WORDS: *Prostate cancer; Spacer; Radiotherapy; Hypo-fractionated radiotherapy.*

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INTRODUCTION

Prostate cancer (PCa) is the second most commonly diagnosed cancer in men, with approximately 1.1 million diagnoses worldwide each year, accounting for 15% of all cancers diagnosed (1). The incidence of PCa increases with age, with over 25% of men over the age of 75 years being affected (1). Low-risk PCa (PSA < 10 ng/ml, ISUP 1, T2a) can be managed through several different modalities, including the non-operative approach of "*active surveillance*", which involves laboratory and clinical monitoring of tumor progression and active treatment if necessary (2). Other active treatments, such as radiotherapy or surgery, are also options. Intermediate/high-risk organ-confined prostate cancers require active treatment, which may include surgery and/or radiotherapy (external beam or brachytherapy). Approximately 40% of people with prostate cancer undergo radiotherapy as part of their treatment, which can serve various purposes such as curative intent, post-operative adjuvant, post-operative rescue intent, or palliative intent (3). Conventional radiotherapy is delivered as *external beam radiotherapy* (EBRT), and conformal radiotherapy, including *3D conformal radiotherapy* (3DCRT) and *intensity-modulated radiotherapy* (IMRT), is commonly used in high-income countries.

During treatment, despite recent advances in techniques and technologies that allow precise delivery of radiation on the focus organ, pelvic radiotherapy inevitably exposes the surrounding normal gastrointestinal tract to some degree of radiation, potentially causing rectal bleeding, ulcers or fistulas and increasing the risk of rectal cancer by 105% over the following decade (4).

Different strategies have been recently adopted and implemented to minimize these complications; one technique aims to fixate the prostate gland during radiation treatment via a rectal balloon to reduce the prostate motion and to make sure the dose delivered to the target volume is efficient., allowing a safer and smaller planning target volume margin as stated elsewhere (5, 6). By using a rectal balloon, the dose exposure to the posterior rectal wall is decreased as opposed to an increased dose to the anterior rectal wall.

Biodegradable balloon spacers are three-dimensional scaffolds that can be implanted between the prostate gland

and rectum to protect the rectum from radiation during radiotherapy. They are commercially available in Europe. A further clinically available technique reduces the rectal dose of radiations using the injection of materials such as hydrogel, hyaluronic acid gels, and collagen between the prostate and rectum, remarkably lessening late-rectum toxicity. Spacers implantation is indeed a minimally invasive surgical procedure guided by transrectal ultra-sound that permit the positioning of biodegradable balloons that can be placed posteriorly to the prostate to increase the separation between prostate and rectum thus protecting the latter from radiations during RT sessions. It demands attendance of a trained physician, qualified to perform this kind of surgery. The procedure takes from 10 to 30 min and can be carried out under local or general anesthesia.
As reported in the EAU 2022 guidelines, "*…a meta-analysis including one RCT and six cohort studies using the hydrogel spacer demonstrated a 5-8% reduction in the rectal volume receiving high-dose radiation…*" (7). Spacers can be implanted in outpatient setting, using local, epidural, or general anesthesia.
A recent study, evaluated the correlation between the use of prostate spacers and the incidence of erectile dysfunction in men with organ-confined prostate cance submitted to hypofractionated radiotherapy (8). The use of spacers allowed to keep pretreatment sexual potency in 62.5% of the cases (8).
A biodegradable balloon spacer is a three-dimensional scaffold made of biocompatible material that is designed to be implanted between the prostate gland and the rectum, prior to the beginning of a radiotherapy program. It is biodegradable and it is actually commercialized in Europe (Figure 1). With the patient in the lithotomy position, and under *transrectal ultrasonography* (TRUS) guidance, an 18-gauge needle is inserted between Denonvilliers' fascia and the anterior rectal wall (Figure 2).
Once the needle is in the correct position, saline water is injected to carry out hydro-dissection and to create a potential space between the prostate and rectum. Implantation time is relatively short, with a mean overall procedure time of 16 minutes (7.8 min) from time of TRUS insertion to TRUS removal; moreover, the biodegradable gel takes an average of 6 to 12 months to absorb once injected in the patients' regions of interest. Reported complications of spacers positioning, although rare, are prostatic abscess, fistulae and sepsis. The aim of this study is to evaluate the safety and efficacy of biodegradable balloon spacer placement in prostate cancer patients who are candidates for radiation treatment.

Figure 1.
Illustration of a biodegradable balloon spacer positioning.

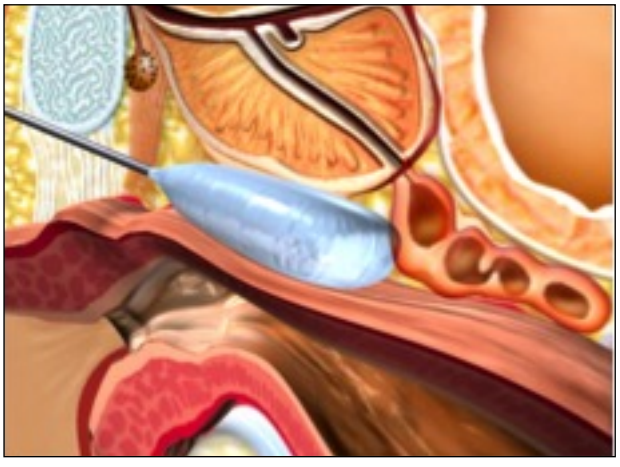
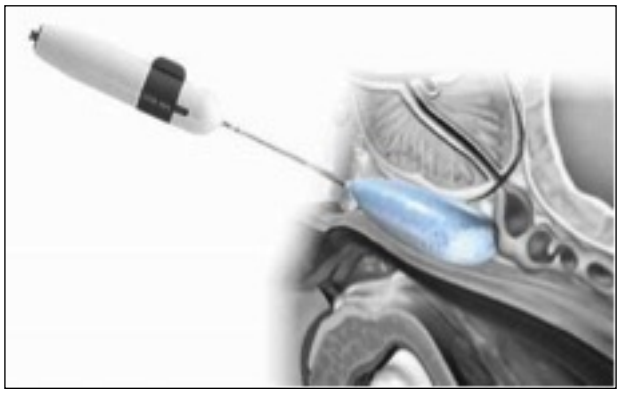


Figure 2.
Illustration of the 18-gauge needle needed for the implantation of the spacer.



Materials and methods

This is a prospective observational study that enrolled patients with a diagnosis of *prostate cancer* (PCa) who had unfavorable/intermediate risk (poor prognosis) and were receiving hypofractionated radiation therapy between January 2021 and June 2022. Patients who had previously received pelvic irradiation for rectum morbidities were also included in the study, and no exclusion criteria were used in the patient selection phase. The timing of the procedure, related complications, and the tolerability of the device were evaluated at two time points: T0 (the day of spacer placement) and T1 (an ambulatory control visit at 10 days). The spacer (*BIOPROTECT® biodegradable spacer*) was placed in an outpatient setting with the patient in a lithotomic position. Cefazoline 1 gram was administered intravenously and local anesthesia was given to the perineal area and levator ani muscles with 2% mepivacaine. The procedure was performed using transrectal ultrasound with a biplanar probe. A cutaneous incision was made at the perineal level, 1 cm above the anus, and the dilator was inserted behind the prostate at the level of the Denonvilliers' fascia. Hydrodissection was performed to create a well-defined plane from the prostate apex to the seminal vesicles. The device containing the balloon was then inserted and advanced to the level of the seminal vesicles, inflated with physiological solution (16-23 ml), and released. The correct positioning of the device was confirmed using *transrectal ultrasound* (TRUS). The patient was observed for any early complications during the post-procedural observation period before being dismissed. Late complications and the tolerability of the device were evaluated at T1. The duration of the procedure (in minutes), observation time (in minutes), and the appearance and severity (according to the Charlson comorbidity index) of early and late complications were

recorded. The tolerability of the device was evaluated using a scale from 0 to 10 for discomfort (0 = no discomfort, 10 = severe discomfort) and by assessing pelvic-perineal encumbrance and changes in bowel function. After the T1 visit, the patient was sent for radiotherapy.

Results

From January 2021 to June 2022, 25 patients were enrolled. Their baseline epidemiological data are shown in Table 1. The procedure was performed in an outpatient setting following the protocol described in the previous section. The average time of the procedure was 18 minutes [10-25 min]. All patients were then discharged within two hours of the procedure (average post-op observation time: 90 minutes [45-110 min]), after the resumption of spontaneous micturition and the absence of early complications. Two patients (8%) experienced acute urine retention that was resolved with catheterization, and one patient (4%) developed a mild perineal hematoma that did not require treatment. As for late complications, one patient (4%) developed fever (> 38°C) the day after the procedure, requiring continuation of the antibiotic regimen. At the T1 visit, no medium-high grade complication was recorded. The tolerability of the device was optimal, with an average score of 2 and a range of 0-4 on the previously described discomfort scale.
No patients reported disturbances in defecation, changes in intestinal transit, or a sense of encumbrance in the pelvic-perineal area. Results are listed in Table 2.

Table 1.
Baseline epidemiologic data.

Patients' characteristics	
Number of patients	25 pts
Age	68 yo (range 59-77)
Tumor stage	cT1c: 10 pts cT2a: 8 pts cT2b: 7 pts cT2c: o pts (0%)
PSA level	14 ng/ml (8-27 ng/ml)
ISUPP	ISUPP 1: 4 pts ISUPP 2: 6 pts ISUPP 3: 15 (%) pts ISUPP 4: 0 (0%) pts ISUPP 5: 0 (0%) pts

Table 2.
Data obtained after the spacer placement.

Average duration of the procedure	18 minutes (10-25 minutes)
Average duration of observation	90 minutes (45-110 minutes)
Early complications	
Acute urinary retention	2 pz (10%)
Hematoma	1 pz (5%)
Late complications	
Fever	1 pz (5%)
Spacer tolerability score	2 (0-4)
Reported bowel symptoms	0 pz
Perineal bulk sensation	0 pz

Discussion

Prostate cancer (PCa) is the second most common cancer among men worldwide, ranking first in developed countries. According to the *World Research Fund International*, there were over 1.4 million new diagnoses of PCa in 2020 worldwide. The incidence and mortality of PCa are correlated with age, with the average age of diagnosis being 66 years. There is a higher incidence of PCa in African-American men compared to white men, with 158.3 new cases diagnosed per 100.000 men and double the mortality. While the lethality of PCa is not as severe as other types of cancer, the number of yearly deaths due to PCa is high due to its high incidence.
PCa diagnosis is based on standardized protocols that involve *prostate specific antigen* (PSA) testing, *digital rectal examination* (DRE), and the newly implemented *multiparametric magnetic reonance imaging* (mpMRI) as an additional diagnostic tool before biopsy, allowing for the specific targeting of possible malignant lesions.
There are various treatment options for organ-confined PCa, ranging from active surveillance to active treatment with surgery or radiotherapy. *Radiotherapy* (RT) can be performed in various settings, such as *external beam RT* (EBRT) and *intensity-modulated RT* (IMRT). IMRT delivers a precise beam of modulated intensity that delivers radiation with higher selectivity to prostatic tissue, minimizing exposure to proximal organs.
An hypofractionated RT protocol uses a higher dose of radiation per session, reducing the number of necessary sessions. The major drawback of RT is the incidental irradiation of proximal anatomical areas, such as the rectum, which is mostly inevitable due to the anatomical relationship between the rectum and prostate. Spacers provide a solution to this problem by inserting a device between the prostate and rectum, separating the target of the radiation beam from a contiguous organ. In addition, the procedure can be performed in an outpatient setting via a day-hospital regimen, resulting in reduced costs and minimal operative time (9).
Overall, the implantation of spacers has been shown to be safe and fast, with optimal tolerability of the device (10, 11). No severe complications were observed in the post-procedural time (T0), allowing the procedure to be performed in an outpatient setting and at T1 follow-up outpatient visit. Mild complications related to the implantation procedure have been documented, but they are relatively uncommon. We recorded one episode of *acute urinary retention* (AUR) in a patient with a voluminous enlarged prostate, a risk factor commonly associated with prostate biopsies.
The incidence of *urinary tract infections* (UTIs) is comparable to that of transperineal prostate biopsies, so adherence to the most recent guidelines is recommended (12). Even among the most unfavorable cases (patients who have already undergone radiation treatment and need another cycle of IMRT), no complications ranging from mild to severe were reported, in contrast to what is suggested in the EAU guidelines about this topic (fistulas, abscesses, sepsis).
Our overall experience is in line with the European consensus, as we did not encounter acute or delayed intermediate-severe complications, despite having modest

previous experience with these types of devices and transperineal procedures. This highlights the low learning curve for this procedure.

Conclusions

Biodegradable balloon spacers appear to be safe and well tolerated and their positioning does not present any technical difficulties or risks of major complications. Its usage can and must be discussed when dealing with patients diagnosed with prostate cancer and scheduled to undergo radiation therapy in order to increase the selectivity of such treatment by protecting the rectum via mechanical separation from the prostate. The device is designed to be left in place as it is biodegradable and does not require any additional maintenance or monitoring.

There are several potential benefits to using a biodegradable balloon spacer in the treatment of prostate cancer. In addition to potentially improving the effectiveness of radiation therapy, it may also reduce the risk of side effects such as rectal bleeding and discomfort. It may also help to reduce the risk of long-term complications such as bowel and urinary incontinence.

Overall, the biodegradable balloon spacers are promising tools in the treatment of prostate cancer, offering the potential for improved outcomes and fewer side effects for patients. It is an important advancement in the field of cancer treatment and continues to be studied and refined in order to optimize its effectiveness and safety.

Nonetheless, further data must be gathered as more of these devices are effectively used in everyday clinical practice to improve our understanding of its efficacy in protecting the rectum from radiation beams and their effects on the quality of life of patients, thus requiring a longer follow-up.

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