A Novel Device for Protecting Rectum During Prostate Cancer Irradiation: In Vivo Data on a Large Mammal Model

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Purpose: Hypofractionation schemes and associated higher rectal doses have evoked the need for improved protection of the rectum during prostate cancer irradiation.

Materials and Methods: An implantable, biodegradable, inflatable, preshaped triangular balloon of commercially used poly(L-lactide-co-ε-caprolactone) co-polymer material was developed to provide separation between prostate and rectum. Biocompatibility and degradability of the balloon implanted subcutaneously or perineally, and in the context of transperineal implantation and local irradiation were evaluated in several in vivo studies.

Results: The device was found to be biocompatible in subcutaneously implanted rabbits up to 42 days, in a transperineally implanted dog up to 12 months and in 8 transperineally implanted pigs up to 6 months. Upon inflation in situ the balloon separated the tissues, remained inflated for several months and subsequently biodegraded. No systemic or local toxicity was noted, as shown by histopathology. Device insertion into the perineal area using a dedicated introductory kit was convenient and feasible. Three-month followup in irradiated pigs that received 15 Gy in 3 fractions 1 week apart showed a stable balloon position with no local or systemic side effects.

Conclusions: This novel device was safe and effective for its intended use of separating tissues for a desired duration. A clinical study will commence to evaluate the safety and efficacy of this device during irradiation in patients with prostate cancer.

Key Words: prostate, rectum, radiotherapy, complications, equipment and supplies

Prostate cancer represents a major public health problem in men in developed countries. In the United States radiation therapy is an option for localized disease. Whether it is implemented with external beam approaches or brachytherapy methodology the responsible physician must be cognizant of the risks assumed by nearby organs (eg rectum and bladder) located in the vicinity of the prostate gland. These risks are accentuated by the treatment methods of intensity modulation and hypofractionation, which expose normal tissue to escalating total doses of radiation or to large daily fractional doses. Implementing either of these methods requires the adoption of techniques that protect structures situated adjacent to the prostate.

It is axiomatic that the dose fall-off of radiation beam intensity from the source is highly influenced by dis-
tance. As such, tactics that can interpose more physical space between the irradiated target, eg the prostate gland itself, and nearby organs, eg rectum and bladder, would minimize the possibility of clinically manifested morbidity. Toward this end an implantable, degradable balloon device was designed to impose separation and increase the distance between the prostate and the surrounding organs. This radio protective strategy was tested in an in vivo large animal model.

The goals of the current experiments were several fold, including to 1) assess the durability and degradability of the device throughout greater than 42 days of followup, 2) determine the feasibility of transperineal implantation of the device and 3) document the safety of the device during and after implantation with and without irradiation. We summarized the findings of the initial experiments done with this device. Plans for future clinical testing are proposed.

METHODS AND MATERIALS

Test Device
An implantable, biodegradable, inflatable balloon that is 10 to 20 mm wide when fully inflated and made of commercially used polyactic acid and caprolactone material in a 70:30 ratio (PLCL) was developed to induce organ separation. These types of copolymers are biodegradable (fig. 1). The starting time of biodegradability can be set to weeks or months after implantation. Thickness of the balloon sheet is in the range of 0.02 to 0.1 mm. Upon inflation with physiological solution balloon width is 10 to 20 mm (fig. 1).

Animal Welfare Arrangements
A protocol was designed in compliance with the guidelines of the Animal Welfare Laws of the State of Israel. Approval to perform the study was obtained from the Tel Aviv Medical Center institutional animal care and use committee, and the Israeli Ministry of Health regulatory board.

All animals were housed in an approved facility under sanitary conditions. The animals were provided with food and water according to local standard operating procedures. The animals were tranquilized and sedated to permit several minutes of intervention for implantation. Transperineal implantation required approximately 15 minutes. The same tranquilizing medication was used for the radiation treatment sessions described. Analgesics were administered after the implantation and radiation sessions to attenuate possible animal discomfort.

We used 3 models of animal implantation. 1) No. 4 PLCL balloons were subcutaneously implanted into each flank of 2 rabbits, which were followed up to 42 days. 2) A similar balloon was inserted through a perineal approach into the perirectal area of 1 dog, which was followed for 1 year. 3) Eight pigs underwent similar transperineal balloon insertion with local irradiation and were followed up to 6 months with the main followup at 3 months.

Transperineal Balloon Insertion
A simple transperineal approach was used to insert and deploy the device using a special delivery system that released the inflated balloon between the anterior rectal wall and the bladder. In pigs and dog the prostate is located intraperitoneally.

The animals were sedated according to local procedures and arranged supine with the perineum exposed. The perineum and anus areas were prepared with antiseptic solution and local anesthesia. The kit includes a needle, a guidewire, a 2 to 3 mm dilator with a sheath passed over the dilator and an introducer that includes the balloon itself inside a second sheath that can be introduced through the dilator outer sheath. The needle, guidewire and dilator with the outer sheath are commonly used as part of a method known as the Seldinger technique. When the outer sheath is located in situ, an inner sheath with the balloon folded inside it as part of the introducing kit is inserted in the outer sheath until it reaches the desired location. At this point the outer and inner sheaths are withdrawn, exposing the balloon at the desired location. Subsequently the balloon is inflated with physiological solution. By retracting the introducer kit the balloon is then sealed to prevent deflation using a biodegradable plug made of the same copolymer that is forcefully placed

Figure 1. A, biodegradable PLCL. B, prostatic balloon was preshaped to separate and retract prostate from nearby rectum.
into a nonelastic biodegradable tube at the balloon orifice. This maneuver seals it watertight until biodegradation has progressed to such a level that the balloon deflates. This period should be at least 42 days to complete the standard irradiation period.

**Radiation Sessions**

The pigs were irradiated at 3 sessions that coincided with days 17, 24 and 30 after implantation. A waiting period was introduced to allow the inflammatory response to resolve. The total cumulative amount of radiation in each pig at these 3 sessions was 15 Gy, that is 5 Gy per session per pig. This was deemed to be biologically similar to the actual radiation that a human rectum might receive when high dose radiation therapy is done.

The pigs were weighed before each session and blood withdrawal was done just before each radiation session. CT of the implant area was performed at each radiation session to evaluate implant durability.

Eight pigs were used, including group 1—2 with implants and without radiation, group 2—2 without implants but with radiation and group 3—4 with implants and radiation. One pig per group was sacrificed for local and systemic histopathology evaluation on day 49 after implantation, 4 were sacrificed on day 90 after implantation and 1 group 3 pig was sacrificed 180 days after implantation.

**RESULTS**

**Biocompatibility and Degradability**

In rabbits the subcutaneously implanted balloon showed complete biocompatibility with no evidence of a local adverse effect at 42 days (fig. 2). In the dog the balloon was transperineally inserted and pathologically evaluated 12 months after implantation.

There were no abnormal histological findings in the urethra or the colorectal mucosa. A single area of macrophage infiltration surrounding proteinaceous material (arrow), compatible with focal foreign body reaction, was noted in implanted dog at 12 months. Reduced from x4.

**Perineal Insertion Feasibility**

The balloon was easily implanted by a urologist (AP) (fig. 4). No acute surgical adverse events were noted, such as perforation, excessive hemorrhage or insertion site infection.

In the pigs correct balloon positioning was evaluated and documented by CT at simulation on day 17.
after implantation (fig. 5, A). Radiation in the pigs was administered according to the described prescriptions (fig. 5, B). No excessive radiation related complications were observed, such as diarrhea, discharge, etc. On day 73 CT in the surviving pigs confirmed no dislocation of the device.

**Histological Evaluation**

One pig per group was sacrificed on day 49. Upon evaluation of the internal organs there were no significant changes among the pigs. Lymph nodes were reactive in all pigs, including the control without the implant, indicating that the findings were incidental and unrelated to the implant.

There was no evidence of toxic insult due to the implant. The fibrous capsule surrounding the implant was within normal limits of what should be expected with any foreign body reaction. Mild lymphoplasmacytic infiltrates were seen but they were not associated with radiation or with the device because they were present in all 3 samples (fig. 6).

Four pigs were sacrificed on day 90. The pathologist described a fibrous capsule surrounding the implant in all 3 implanted pigs. An active inflammatory process was present in the pig that underwent radiation alone (fig. 7). Neither rectal nor urethral damage was observed in any pigs. Long-term surveillance continued in 1 pig that was treated with implantation plus radiation. The pig was maintained in good condition until sacrifice at 6 months with no late side effects observed.

**Figure 5.** A, correct positioning of balloon (black arrow) was documented by CT at simulation on day 17 after implantation in pig. B, irradiation consisted of 15 Gy in 3 fractions of 5 Gy each 1 week apart in 4 oblique beams directed to tissue surrounding balloon.

**Figure 6.** Histological evaluation of implanted and irradiated pig at day 49. A, dorsal implant area adjacent to rectal wall showed mucosal epithelium erosion, mild edema and mild diffuse lymphocyte infiltration. Reduced from ×4. B, in ventral implant area there were small mineralization foci, minimal fibrosis and few macrophages laden with basophilic material at edge of fat section. Reduced from ×2.
Radiotherapy strategies for the curative management of prostate cancer have become more common in the last decade. With regard to external beam radiotherapy the primary complication is related to rectal damage. Toxicity pertaining to the latter rarely leads to frank ulceration, although some degree of rectal toxicity may occur in up to a fifth of patients. As defined by Radiation Therapy Oncology Group grades 1 to 3 or Common Toxicity Criteria, proctitis is still prevalent in most modern series that emphasize meticulous followup. In such patients quality of life may be disrupted by inflammatory pain, soiling, loss of mucus and stool incontinence. Accordingly the desire to optimize the therapeutic index in patients with prostate cancer served as an impetus for the design of this novel approach.

Historically multiple concepts have been brought forward to contend with the problem of rectal morbidity. The time honored approach of shaping the radiation field by interposing a protective block augments the risk of simultaneously blocking tumor, thereby compromising the ability to achieve control by radiotherapy. Optimized planning techniques with intensity modulated and image guided radiotherapy have been proposed as a creative means of minimizing the rectal dose. The benefit of these strategies will become known after longer followup becomes available. Insertion of a rectal balloon every day before the radiation session was found to be an effective mode to decrease late side effects. However, inconvenience and a possible increase in immediate side effects limited its wide use.

A recent report documents HA injection into the perirectal fat to increase the distance between the prostate and the anterior rectal wall. In a study of 27 patients with prostate cancer treated with a combination of intensity modulated radiotherapy and high dose rate brachytherapy 3 to 7 ml HA were injected under ultrasound guidance to create a 1.5 cm gap in the described space. Followup imaging with CT and magnetic resonance imaging revealed no migration or changes in shape of the substance. Moreover, the investigators achieved a significant decrease in the rectal dose during brachytherapy. In response to this article Vordermark et al raised the possibility of the long-term side effects that HA may initiate as a foreign material. Moreover since HA was documented to be unchanged and in place for up to 1 year, they suggested using a shorter lived material, possibly body fluids, such as patient blood. Indeed, Morancy et al recently reported on 3 patients who underwent a blood patch to decrease the rectal dose during 131 cesium prostate brachytherapy.

The currently described device is similar to HA injection and the blood patch in that it achieves good separation of the anterior rectal wall from the surrounding tissue. In the clinical setting its advantages over HA injection and the blood patch are its preshaped features, degradability for different periods and possible use for image guided radiotherapy. In this study we documented the biocompatibility of the device in a total of 4 subcutaneously inserted implants in 3 pigs. Fibrous capsules surrounding the implant were noted in all 3 pigs. Active inflammatory processes were noted in one pig that received radiation alone. Reduced from ×10 and ×4.

**Figure 7.** A, fibrous capsule surrounding implant was noted in all 3 pigs. Reduced from ×10. B, active inflammatory process was present in one that received radiation alone. Reduced from ×4.
implants in 2 rabbits for up to 42 days and in 1 transperineal implant for up to 12 months. No local or systemic side effects were noted. Biodegradability was documented (almost reabsorption) in 1 implant at 12 months. Adding local irradiation to the biocompatibility of the device was examined and no local side effects were noted in nearby tissues. In addition, the feasibility of transperineal insertion and implantation of the balloon, and its nondislocation for 3 months were demonstrated.

**CONCLUSIONS**

This novel device was found to be safe and effective for achieving its intended use of partitioning between tissues with and without irradiation for a desired time. The described product can potentially alleviate or even eliminate most rectal side effects. After observing the in vivo feasibility of this new system we received approval from our institutional review board to perform a clinical trial with the device in men with prostate cancer.

**REFERENCES**


