Barrigel®
BY PALETTE LIFE SCIENCES

PROSTATE RADIATION THERAPY TREATMENT PLANNING with Barrigel

USER GUIDE

ABOUT BARRIGEL

Barrigel is a biodegradable gel made of Non-Animal Stabilized Hyaluronic Acid (NASHA®), and is FDA-cleared, CE Marked and approved by the Australian Therapeutic Goods Administration for prostate-rectum separation when treating prostate cancer with radiation. NASHA gel provides both sculptability and lift, making it an ideal material for spacing. NASHA products have been in medical use for over 2 decades in more than 50 million procedures worldwide.[1]

BIOLOGIC MATERIAL

Hyaluronic acid is a natural component of biologic extracellular and connective matrix for the maintenance of proper structure and function of tissues by creating volume, lubricating tissues and enhancing mobility. The physiological function of hyaluronic acid stems from the large size and hydrodynamic volume of its hydrophilic molecular network. This glycosaminoglycan-based polymer forms a mesh with the capacity to hold large amounts of water. The unique aspect of NASHA is the way the hyaluronic acid molecules are joined and entangled to create an especially stable 3-dimensional molecular network, which defines it as a gel.[2]

CREATION OF SPACE

The gel is injected into the patient's perirectal space under transrectal ultrasound (TRUS) guidance, usually during the same procedure that is performed to insert fiducial markers. The gel appears dark (hypoechoic) and is easily visible on TRUS. It remains malleable and may be sculpted with the needle to achieve an even and symmetric implant around the posterior prostate. The goal is generally to create approximately 1 cm or more of separation from base to apex, and in some cases, separation around the seminal vesicles may be desired. Precise measurements of the space may be taken during the procedure on the TRUS image, which, in addition to the total volume injected, may be of use to the treatment planning team as they contour.

STABILITY

Since Barrigel is composed of biodegradable material, it is completely absorbed by the patient's body over time. It has been formulated specifically to maintain stable space for the entire course of prostate radiotherapy treatment.[3]

To achieve optimal outcomes for patients with the Barrigel rectal spacer, consider the following treatment planning best practices recommended by sites participating in the Barrigel Prostate Trial.

TREATMENT PLANNING

These steps are based on best practices, most of which are appropriate for any prostate plan. For Barrigel, the key to achieving excellent results is to learn to push the optimizer to get more rectal sparing than is commonly seen without spacers. **The goal is to take advantage of the additional space by dropping the dose gradient steeply across it.** There are a few tips to lay the groundwork.

Please follow your institutional guidelines, clinical experience, and training first and foremost. These best practices have been collected to assist you in exploring ways to get to an acceptable plan efficiently but are not a substitution for any of the above. Every patient is different, and expert clinical judgement is always required.

IMAGING FOR PATIENTS WITH BARRIGEL

Consistency with daily set-up is key, as it would be for any patient. The Barrigel location, shape and volume will remain consistent in the body from shortly after the implant to the duration of the radiotherapy course and some months beyond.[3] To keep the rest of the pelvic anatomy as consistent as possible, **patients should be instructed to have a comfortably full bladder and empty rectum** for the CT simulation image set, MRI simulation image (if used) and for each treatment session, or as per the standard bowel preparation in your institutional practice. **Proper bowel prep is crucial.**

MRI

A post-implant MR image is not required but can enhance the ability to distinguish prostate and gel borders for ease in contouring. A T2 weighted sequence is optimal for gel visualization and anatomic localization. **Barrigel will appear bright white in this sequence.**

Recommended parameters for MR: Axial T2 proton weighted acquisition to include iliac crests through the perineum with a slice thickness of 3-5 mm.

CT Simulation

For acquisition of the Simulation CT image set, make sure the slice thickness is small enough to get adequate spatial resolution in the region of interest; **a maximum of 3 mm is recommended**. Remember the Barrigel implant is only 1-2 cm in width (AP), and as approximately long as the prostate in length (S-I). Note that the gel is **tissue-equivalent density**, so the default standard Hounsfield unit mappings are appropriate.

TREATMENT PLANNING GUIDELINES FOR BARRIGEL

Having the additional distance provided by the gel at the prostate-rectum interface may seem like it simply makes planning with usual constraints easier. **However, pushing optimization techniques can often make a new level of rectal sparing possible.** Explore these suggestions from expert Barrigel users:

1. CT-MR Fusion

a. If an MR image with Barrigel is present in addition to the simulation CT, fuse them to fiducial markers first.

b. Ensure the prostate, bladder and rectal interfaces are aligned. If the fusion is well-matched through this volume, use the MR to guide the contouring of Barrigel.

c. The prostate and seminal vesicles may also be contoured on the MR, with refinement on the CT as needed.

2. CT-only Planning

a. **Targets:** If there is no MR for the patient, contour the prostate first and add the CTV and PTV target volumes, as usual. You will notice a slightly less dense (dark) layer, usually a flattened oval mass of "space," between the anterior rectal wall and the posterior prostate wall. This is effectively a 1 cm or more buffer zone. When in doubt, if the exact prostate border is difficult to infer, it is not problematic to extend a little into the gel region.

b. **Organs at Risk (OARs):** Next, contour the length of the rectum in relationship to your PTV. Ensure that the contours are close to anatomic borders of the rectal wall. Complete the other OAR contours, per institutional guidelines.

c. **Gel:** Knowing the exact dose to gel is not of biological significance, but most sites will want to define it as a structure. Spotting the general region of the gel is generally not difficult, but like many structures it can take some experience to discriminate the edges of the implant, since Barrigel has a tissue-like density. An ideal injection will lead to an approximately symmetric implant centered on the midline, with a flattened oval cross section 1-2 cm wide at the middle (minor axis). It should taper off smoothly with rounded edges to each side on the axial view (**Figure 1**A), extending on all the slices from prostate base to apex. Sometimes several distinct boluses are seen, as in the second image below (**Figure 1**C). **Do not attempt to contour individual boluses; focus on capturing the overall volume of space created.** If desired, you may get both the volume of the prostate and volume of the gel from the TRUS images.

3. Example Beam Configurations

a. **VMAT:** Typically, best results are obtained with two arcs, one with CCW rotation and one CW rotation. Experiment with collimator angles. Unequal angles (e.g., 350° and 40°) may yield more flexibility with dose control than beams with collimator angles closer to each other (e.g., 15° and 345°). Consider avoiding collimator angles of 45° and 315° as these generally create the greatest amount of low-dose leaf leakage.

b. **Static IMRT:** Try 7-9 beams, collimating along the slope of the rectum while avoiding collimator angles of 0-5° to avoid overlap of interleaf leakage doses.

4. Dosimetry Optimization Tips

No heterogeneity correction is needed

a. Try to have the **30%/50%/90% isodoses flow parallel to posterior prostate contour** and bisect the rectum with at least the 50% isodose line, and if possible, the 30% isodose line.

b. Defining special optimization structures can help the optimizer meet these goals. Some suggestions include the following:

i. Create a structure 1 mm larger than the actual PTV **("PTV_OPT")** and optimize to this instead of the PTV itself. Manually edit the volume away from rectum if the size is excessive due to the 3D-expansion.

ii. Create a smaller structure for the rectum **("Rectum_OPT")** that extends only 2 CT slices superior and inferior to the PTV and optimize to this structure.

iii. Create a structure **"Avoid_Rectum"** from **"Rectum_OPT"** by expanding it 2-3 mm, deleting superior and inferior slices beyond the **"Rectum-OPT"** structure, and then crop it away from **"PTV_OPT"** by 1 mm. Give higher priority to this structure with fairly low dose constraints, including using mean dose function if available.

iv. Create a structure **"Avoid_Post"** from the **"Avoid_Rectum"** structure by expanding it ONLY posteriorly until it exits the body, then crop it to the posterior patient surface, as well as cropping it 1.2 cm from **"PTV_OPT."** Next, crop the **"Avoid_Rectum"** from **"Avoid_Post"** by 0 mm, and then crop **"Avoid_Post"** from **"Avoid_Rectum"** by 1 mm (so they do not overlap). Use this to help minimize rectal/posterior dose even further.

v. Create **"Avoid_Bladder"** by expanding bladder 2-3 mm and crop away from **OPT_PTV** 7 mm. Crop it out of **Avoid_Rectum** and **Avoid_Post** to prevent overlap. Use this to help control the bladder dose further.

vi. Create **"Avoid_Penis"** where the penile shaft will receive dose and use this to minimize it.

vii. Create 2 or 3 ring structures around the PTV at varying distances but cropped out of the optimization structures so none are overlapping. This can help with tighter high-dose conformality as well as reduce mid- and low-dose streaking. Don't over-prioritize rings at the expense of the rectum.

c. Note suggested planning structure priority order as follows:

i. Prostate V100 > 98%

ii. Minimize Rectum D90

iii. Bladder V60 < 5%, may not always be met depending on overlap with PTV

5. How much rectal sparing is achievable?

A reasonable goal for well-optimized prostate plans is that the dose gradient from the target should decrease roughly 10% per mm of distance. Your experience may vary, but with best practices it is possible to achieve excellent rectal sparing.

CT VISIBILITY WITH BARRIGEL

Figure 1 A,B,C,D,E

An illustration of the nominal appearance of prostate, Barrigel and rectum (**1**A), along with two example patients with Barrigel implants (**1**B, **1**C). In these axial CT slices Barrigel appears as a slightly less dense (darker gray) rounded layer of gel between the prostate and rectum.

i. Window and level optimization is important and can help bring out subtle density and texture differences. **Try using the presets for Liver/Cerebellum. This often enhances the Barrigel borders and the rectal wall** (**Figures 1**D and **1**E). Expect Barrigel to be slightly darker gray than surrounding tissues in the axial view.

ii. Remember, the goal of this plan is to take advantage of the space between the rectum and prostate by getting the dose gradient to drop steeply across it. **Some imprecision in defining the border of the gel is tolerable, as the quality of the plan will be driven by the target coverage and rectal sparing.**

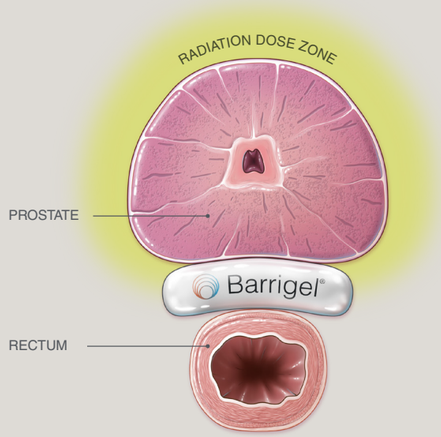


Figure 1A

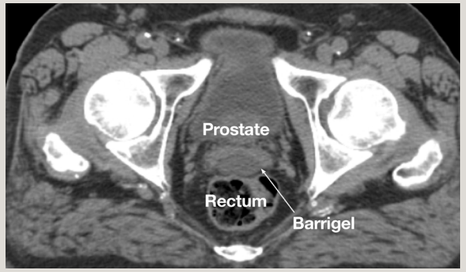


Figure 1B **CT image** courtesy of Escalarta López Ramírez, MD, GenesisCare Spain
Radiation Oncologist; Madrid, Spain

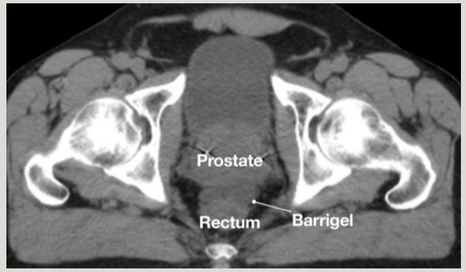


Figure 1C **CT image** courtesy of Glen Gejerman, MD New Jersey Urology
Radiation Oncologist; New Jersey, United States

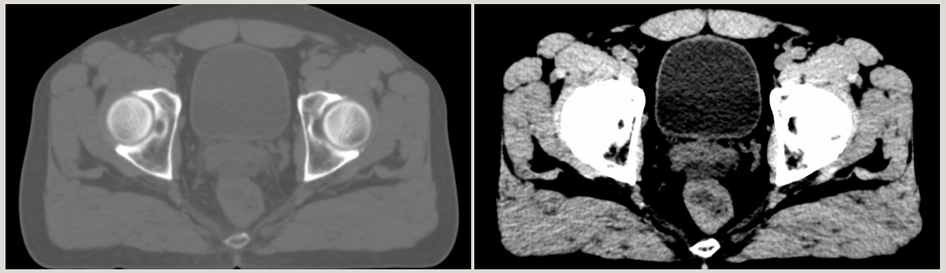


Figure 1D **Before (left)** and **after (right)** adjusting window & level settings to enhance contrast and texture

CT images sourced from the Barrigel Prostate Trial

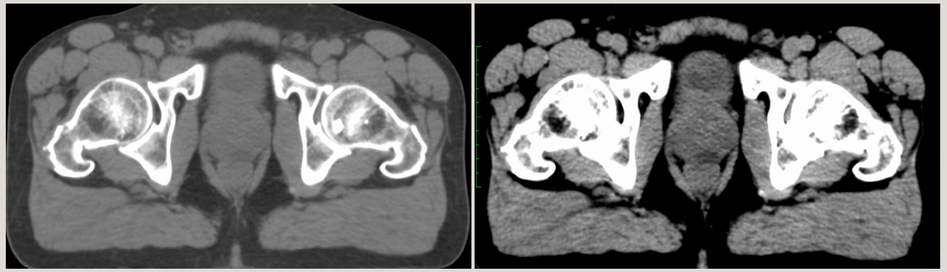
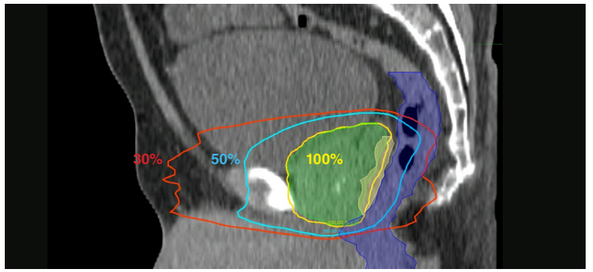


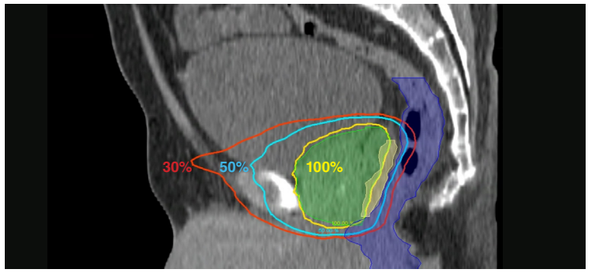
Figure 1E **Before (left)** and **after (right)** adjusting window & level settings to enhance contrast and texture

CT images sourced from the Barrigel Prostate Trial

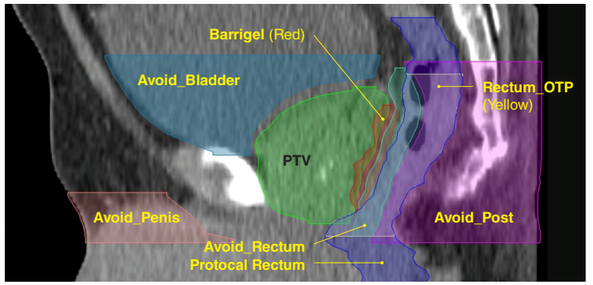
PANEL 2A) Suboptimal Post-Gel Plan: 30% Encompassing Rectum



PANEL 2B) Improved Plan: 30% And 50% Lines Bisecting Rectum



PANEL 2C) Example Optimization Structures



Panel 2 A,B,C

Demonstration of the use of optimization structures to create a dose gradient that takes advantage of the space between the prostate and rectum to maximize rectal sparing.

Panel 2A**)** shows a somewhat standard but suboptimal plan with the 30%, 50% and 100% isodoses. (Barrigel contour not shown)

Panel 2B**)** shows the same patient with an optimal plan, achieved by using the illustrated optimization structures.

Panel 2C**)** see Step 4B for description

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3. Mariados NF, Orio PF, Schiffman Z et al. Hyaluronic acid spacer for hypofractionated prostate radiation therapy: A randomized clinical trial. *JAMA Oncol.* 2023: e1-e8.

FURTHER LITERATURE

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4. Prada PJ, Fernández J, Martinez AA, de la Rúa A, Gonzalez JM, Fernandez JM, Juan G. Transperineal injection of HA in anterior perirectal fat to decrease rectal toxicity from radiation delivered with intensity modulated brachytherapy or EBRT for prostate cancer patients. *Int J Radiat Oncol Biol Phys.* 2007 Sep 1;69(1)95-102.

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BARRIGEL® is used to position the anterior rectal wall away from the prostate during radiotherapy for prostate cancer, with the intent of decreasing radiation dose delivered to the rectum. The product should be injected into the anterior perirectal fat. BARRIGEL shall only be administered by qualified and properly trained physicians with experience in ultrasound guidance and injection techniques in the urogenital/pelvic area. Barrigel is contraindicated in prostate cancer patients with clinical stage T4 disease.

As with any medical treatment, there are some risks involved with the use of BARRIGEL. Potential complications associated with the use of BARRIGEL include, but are not limited to: pain associated with BARRIGEL injection; needle penetration of the bladder, prostate, rectal wall, rectum, or urethra; injection of BARRIGEL into the bladder, prostate, rectal wall, rectum, urethra, or intravascularly; local inflammatory reactions; infection; urinary retention; rectal mucosal damage, ulcers, necrosis; bleeding; constipation; and rectal urgency. More information on indications, contraindications, warnings and instructions for use can be found in the Instructions For Use at www.barrigel.com, www.barrigel.com.au or www.barrigel.eu.

U.S. CAUTION: The law restricts these devices to sale by or on the order of a physician.