
# Teaching Case: Successful Salvage Brachytherapy after infusion of Gold Aurashell nanoshells for Localized Prostate Cancer in a Human Patient

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**Teaching Case: Successful Salvage Brachytherapy after infusion of Gold Aurashell nanoshells for Localized Prostate Cancer in a Human Patient**

**[Short Running Title]**
Salvage Brachytherapy after Nanoshells

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ABSTRACT:

Prostate cancer is the 4th most common cancer worldwide and a leading cancer diagnosis among men. Conventionally, radiation therapy with brachytherapy is a prevailing standard of care for prostate cancer but is associated with side effects caused by toxicity to adjacent tissues. In recent years, there have been advancements in new cancer treatments to minimize damage to surrounding organs, including Aurolase Therapy, which has demonstrated successful tumor removal through targeted ablation in clinical trials. This emerging technology involves focal therapy using gold nanoshells. While using radioactive nanoparticles in brachytherapy as an alternative to traditional seed implants has effectively reduced tumor size in pre-clinical studies, the combined application of seed implants and nanoparticles in a human subject has never been attempted until now. We report the first known case of a patient treated with brachytherapy after administration of gold nanoshells, who now shows neither persisting cancer nor unexpected side effects that could be attributed to the combinatorial therapy 1-year post-treatment. Given the lack of complications over brachytherapy alone, salvage brachytherapy in persons receiving gold nanoshells is feasible, and the combination could potentially have a therapeutic benefit.

INTRODUCTION:

Prostate cancer is the second most common malignancy in men with multiple treatment options ranging from active surveillance, radiation, and surgery depending on comorbidities and cancer staging.[1 2] Brachytherapy can be an attractive treatment option for prostate cancer, given shortened treatment time and equivalent outcomes to surgery, particularly in the early-stage localized setting.[3 4] However, brachytherapy is characterized by more acute urinary irritation compared to other therapies in the initial six months following treatment, although the symptoms steadily improve and generally resolve within a year.[5 6]

Focal prostate cancer treatment options based on nanoparticles are under investigation, intending to target lesions focally at a cellular scale to potentially reduce toxicity on adjacent tissue and, in turn, risks of urinary, bowel, and erectile dysfunction.[7 8] One emerging technology exploits the ability of intravenously infused gold nanoshells (AuroShell, Nanospectra, Houston, Texas) to accumulate passively in tumor tissue via the enhanced permeability and retention effect. The particles do not accumulate in healthy tissue as they cannot access normal vasculature and instead are cleared from the bloodstream by the reticuloendothelial system. AuroShell particles are comprised of a thin gold shell, 10 to 20 nm thick, deposited on a solid silica (silicon dioxide) core. To prevent aggregation of the particles in a saline environment and to provide steric hindrance in vivo, a 5,000 molecular weight (MW) methoxy-polyethylene glycol (PEG) chain is attached through a thiol (sulfur) bond. The PEG coating improves the stability of the AuroShell particles in an isotonic aqueous solution and may also enhance the circulating half-life on administration. When illuminated with a near-infrared light source, these accumulated nanoparticles absorb and convert the light into heat, causing selective hyperthermic cell death through thermal ablation without affecting non-tumorous tissue. Following treatment, the particles are cleared through the liver or sequester in the liver and spleen with no known side

effects.[9] Ablation of tumors using Auroshells was effectively demonstrated in cell studies and animal models, as well as a clinical pilot study treating men with prostate cancer. It is the only inorganic material that is FDA-approved for photothermal therapy.[7] [10] [11] [12] We report on the toxicity and short-term efficacy for a single patient, who had gold nanoshells accumulated in the prostate gland, and afterward was treated with LDR brachytherapy using Pd-103. The patient consented to the administration of gold nanoshells during a clinical trial (ClinicalTrials.gov Identifier: NCT04240639). Although the trial's intent was to excite the infused nanoshells with the interstitial placement of a near-infrared light source in the prostate gland, technical difficulties prevented the placement of the specialized trial catheters required for light excitation. The patient elected to proceed with a standard-of-care prostate LDR brachytherapy procedure instead. Post-treatment follow-up up to 1 year revealed neither biochemical recurrence nor toxicity or health-related quality of life different than what was expected for brachytherapy.

CASE PRESENTATION:

A 57-year-old white male was referred for urologic consultation after a routine screening. PSA was found to be 4.34 ng/ml in February 2018. He had a multi-parametric Pelvis MRI in March 2018, negative for suspicious prostatic foci. He reported moderate obstructive symptoms with weak force of stream, nocturia of 1-2x, and a sense of incomplete bladder emptying. His DRE indicated a symmetric prostate of 40 GM with no nodules. The patient deferred biopsy and continued to be followed by his urologist when in October of 2019, his PSA rose to 5.58 ng/ml, with no change in his voiding symptoms and lack of irritative complaints. He elected to undergo a transrectal ultrasound-guided prostate biopsy in December 2019. His PSA doubling time using the log slope calculation at the time of biopsy was 68 months. The biopsy revealed a prostate

volume of 33.5 ccs (height 29 mm, width 46mm, length 47 mm), PSAD 0.17, with no nodules or calculi, normal seminal vesicles, and a small middle lobe. The biopsy reported 3 out of 12 cores positive with 5% involvement of core biopsy material with Gleason's grade 3+3 prostatic adenocarcinoma in the right mid apex, 30% involvement in the left middle base, and 5 to 10 % involvement in the left mid apex of the prostate. No angiolymphatic or perineural invasion, significant inflammation, or evidence of atrophy was noted. He was stratified as having NCCN low-risk, Gleason 3+3 clinical-stage t1c prostate cancer, and elected for active surveillance.

A follow-up MRI on 12/16/2020 showed a 1.4x1.1 cm T2 hypointense lesion (Figure 1), demonstrating restricted diffusion (Figure 2) and early postcontrast enhancement in the anterior apical gland adjacent to the fibromuscular stroma suspicious for prostate cancer (Figure 1). This was characterized as a PIRADS-4 lesion. He underwent a targeted trans-perineal prostate biopsy using the UroNav System (Phillips) in early 2021, revealing all 3 of the targeted cores as Gleason 3+4. In contrast, the remaining cores from the conventional 12-core standard biopsy were benign. The patient was interested in pursuing a nanoparticle focal therapy-based clinical trial. He signed informed consent and enrolled in an open-label, multi-center, single-dose study of AuroLase Therapy for the focal ablation of prostate tissue via AuroShell nanoparticle-directed thermal ablation (Nanospectra, Houston, Texas USA; ClinicalTrials.gov Identifier: NCT04240639).

In May of 2021, he received an intravenous infusion of up to 7.5 ml/ Kg of AuroShell particles concentrated to 100 Optical Density (approximately 2.77x1011 particles/ mL or 36 mg particles/ kg of patient weight with a plan for transperineal focal therapy the next day. The planned,

interstitial focal treatment had to be aborted due to unforeseen equipment limitations, which disabled the appropriate placement of the light-source catheters in the pattern required by the study. After consultation with both urology and radiation oncology, the patient weighed alternative options, which included but were not limited to radical prostatectomy or various forms of radiation therapy. The patient was not interested in pursuing radical prostatectomy but was interested in radiation therapy options. The patient was informed that the combination of AuroShell gold nanoparticles and salvage radiation had not been attempted previously and that there could be risks to the procedure that would be unknown. The treating physicians judged that, despite the unknown risks, it was improbable that pursuing immediate radiotherapy would result in toxicity beyond what was expected for the brachytherapy procedure. After informed consent was obtained, the patient agreed to proceed with a standard-of-care LDR brachytherapy implant using Pd-103 sources prescribed at 125 Gy to the periphery of the prostate gland.

A PSA value drawn before the procedure was 9.0 ng/ml. The brachytherapy procedure began approximately 19 hours after his infusion of gold nanoshells and was completed in an additional 2 hours without incident. The brachytherapy procedure utilized 25 needles to deliver 81 sources of 2.62 Units/seed of Pd-103. The total implanted radioactivity was 212.22 Units. Post-implant dosimetry was performed on post-op day 1, revealing a target V100%= 98.66%, D90%=137.08%, and a rectal V100%=1.67%, D1cc=79.86% (Figures 3, 4, and 5).

He responded well to treatment with no adverse effects. He was started on tamsulosin 0.4 mg PO BID after the procedure to reduce lower urinary tract symptoms anticipated after the implant. The patient had a PSA nadir of 0.21 at four months after therapy. His most recent PSA was 0.33

at eleven months following treatment. The patient also had a pretreatment total testosterone value of 857, measured to be 736 at 11 months following treatment.

At his 6-month follow-up visit, the patient reported no change in urinary frequency, a weaker stream, and occasional mild urinary incontinence, which did not require using pads.

At 1-year post brachytherapy, the patient subjectively reported an overall high quality of life. He stated that his perception of orgasm strength was weaker compared to pretreatment, while his nocturia x 1-2 and urinary bother were similar to the pretreatment baseline. Overall, he has no trend toward biochemical recurrence or persisting side effects that significantly impact his quality of life. Table 1 summarizes his pre and post-treatment health-related quality of life surveys including AUA, SHIM, and Merrick scores for urinary, sexual, and bowel function respectively.[13] [14] [15] The table also includes EPIC-CP scores quantifying incontinence, irritative, rectal, sexual, and hormonal symptoms.[16] All of these scores are stable from his pre-treatment values. He does continue to take tamsulosin 0.4 mg PO BID.



DISCUSSION:

There are several definitive treatment options for localized prostate cancer, including radical prostatectomy, various forms of brachytherapy, and focal therapy,[1] but they have a risk of heightened urinary, bowel, and sexual dysfunction.[5] Human clinical trials currently exist that use focally-directed light on tumors to thermally ablate them with millimeter precision. The light excites in-vivo gold nanoparticles that are located near the tumors.[7] [10] [11] Nanoparticles are

generally defined as having a diameter between 1 and 100 nanometers, a size that sits between atomic and molecular diameters, which accounts for their unusual properties.

The use of intratumorally injected radioactive nanoparticles, termed "nanobrachytherapy," is an area of current research interest and has been performed in animal models.[10] [11] Furthermore, there is a well-studied history of using intratumorally injected, radioactive, nanoscale, colloidal gold (Au198) in men with prostate cancer by directly injecting the gold into the prostate gland.[17] In 1950, Dr. Rubin Flocks at the University of Iowa had originally intended to perform a gold-encapsulated radon seed implant on an 80 year patient with prostate cancer. When it was discovered that the radon seeds were unavailable mid-procedure, he substituted 60 mCi Au198 colloid into the tumor. He noted tumor regression on follow-up and, after that, performed and published on the outcomes of over 1500 patients with this technique.[17 18] Although intratumorally injected, radioactive, colloidal gold had proven therapeutic benefits, it fell out of favor as modern external beam and brachytherapy procedures emerged after the 1970s. The light absorption properties of gold nanoparticles are being leveraged in AuroLase Nanospectra Therapy, an ongoing multi-site clinical trial developing ultra-focal tissue ablation therapy for prostate tumors. Nanoparticles, composed of a gold metal shell and a non-conducting silica core, are delivered intravenously and accumulate in the tumor. An interstitial fiber optic probe emits near-infrared laser energy to the nanoparticles, which convert the light into heat that thermally ablates the tumors. By passing ionizing radiation over the nanoparticle density structures to activate the removal of secondary electrons, it may be possible to amplify the effect of radiation and create a high dose adjacent to the nanoparticles. Clinical trial results showed successful focal ablation of low to intermediate-grade prostate tumors in 15 patients, using laser-excited gold-

silica nanoshells in combination with magnetic resonance-ultrasound fusion imaging. 87.5% of lesions in the ablation zone were negative for tumor at 12 months following treatment.[7]

Through selective ablation of the tumor and surrounding blood vessels, AuroLase Therapy hopes to reduce toxicity and systemic side effects that might otherwise occur through more conventional approaches.[7 8] The initial trials of this emerging technology are being investigated in the early stage, focal ablation setting. Aside from the goal of ablating cancer, it is hoped that this approach would preserve the ability of practitioners to safely perform a salvage procedure with surgery or radiation if persistence or recurrence of disease were detected.

We report on the first patient to receive salvage radiation therapy after the infusion of Auroshell nanoparticles. Due to technical difficulties, the patient could not receive the light-excitation treatment component and proceeded to a conventional whole-gland Palladium-103 brachytherapy implant. Although nanotherapy and brachytherapy have been shown to be safe and effective therapies separately, there was a risk that the gold nanoparticles could have acted as a radiosensitizer, leading to increased toxicity when combined with seed implants. However, considering the lack of complications in the treated patient, this combinatorial therapy of nanoparticles and brachytherapy radiation has the potential to be safe and effective at eradicating cancer.



CONCLUSION:

This case report documents the potentially safe and effective use of salvage ionizing radiation via brachytherapy after infusion of gold nanoparticles, resulting in a biochemical response without sacrificing the quality of life. We detail the safety of salvage brachytherapy after gold nanoshell infusion. Persons who undergo nanoshell infusion may consider brachytherapy as a salvage

option if they cannot complete the light stimulation aspect of the therapy or have persistent cancer after completing Aurolase therapy. A clinical trial is required to fully determine the safety and efficacy of combining nanoparticles with salvage brachytherapy and further investigation is warranted, given the lack of serious complications or deleterious impact on genitourinary, bowel, and sexual function in this patient.

## Conflict of Interest

The authors declare that this research was conducted without potential conflicts of interest, including commercial or financial considerations.

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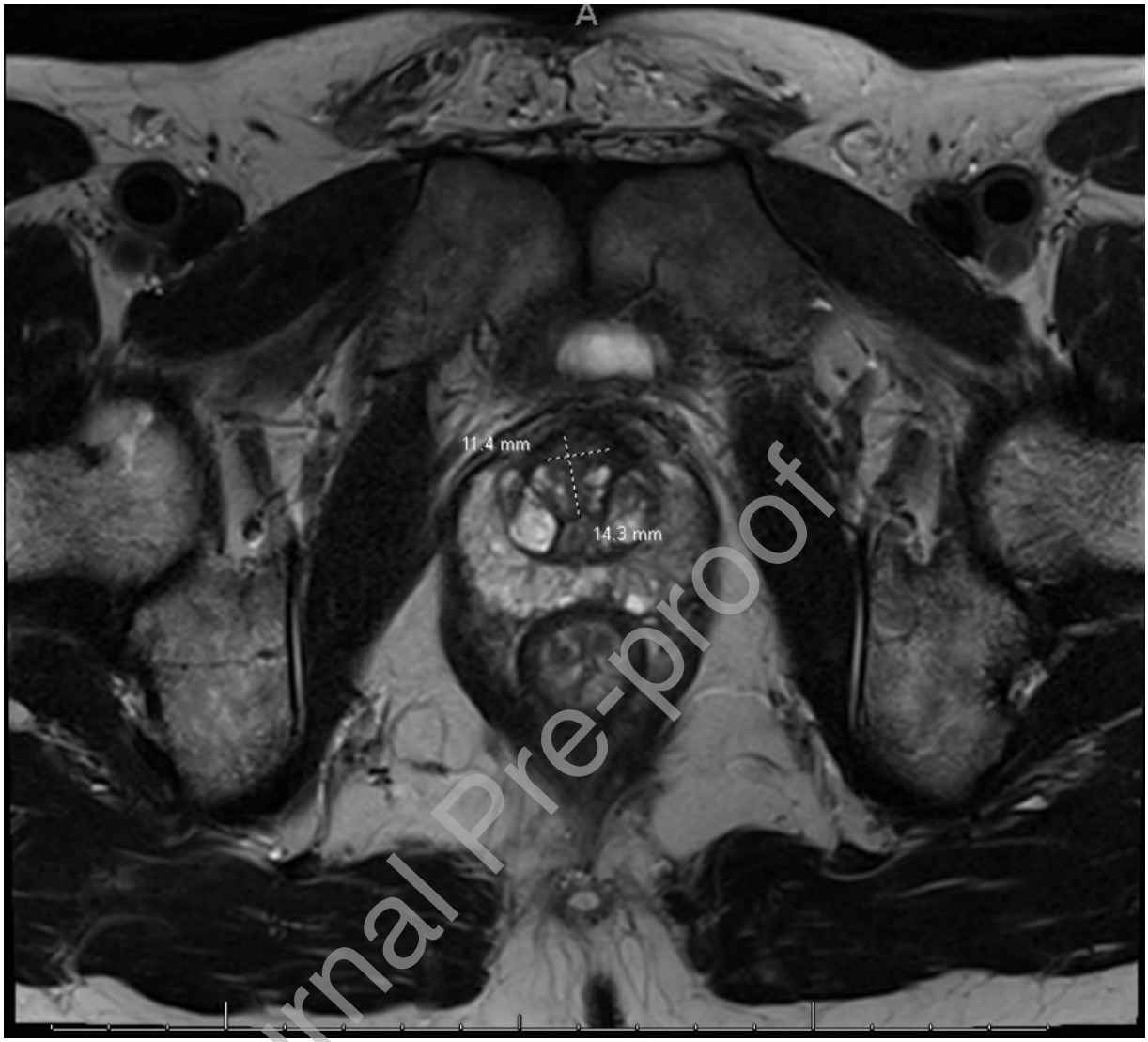


Figure 1. T2 weighted small field of view MRI revealing anterior lesion.

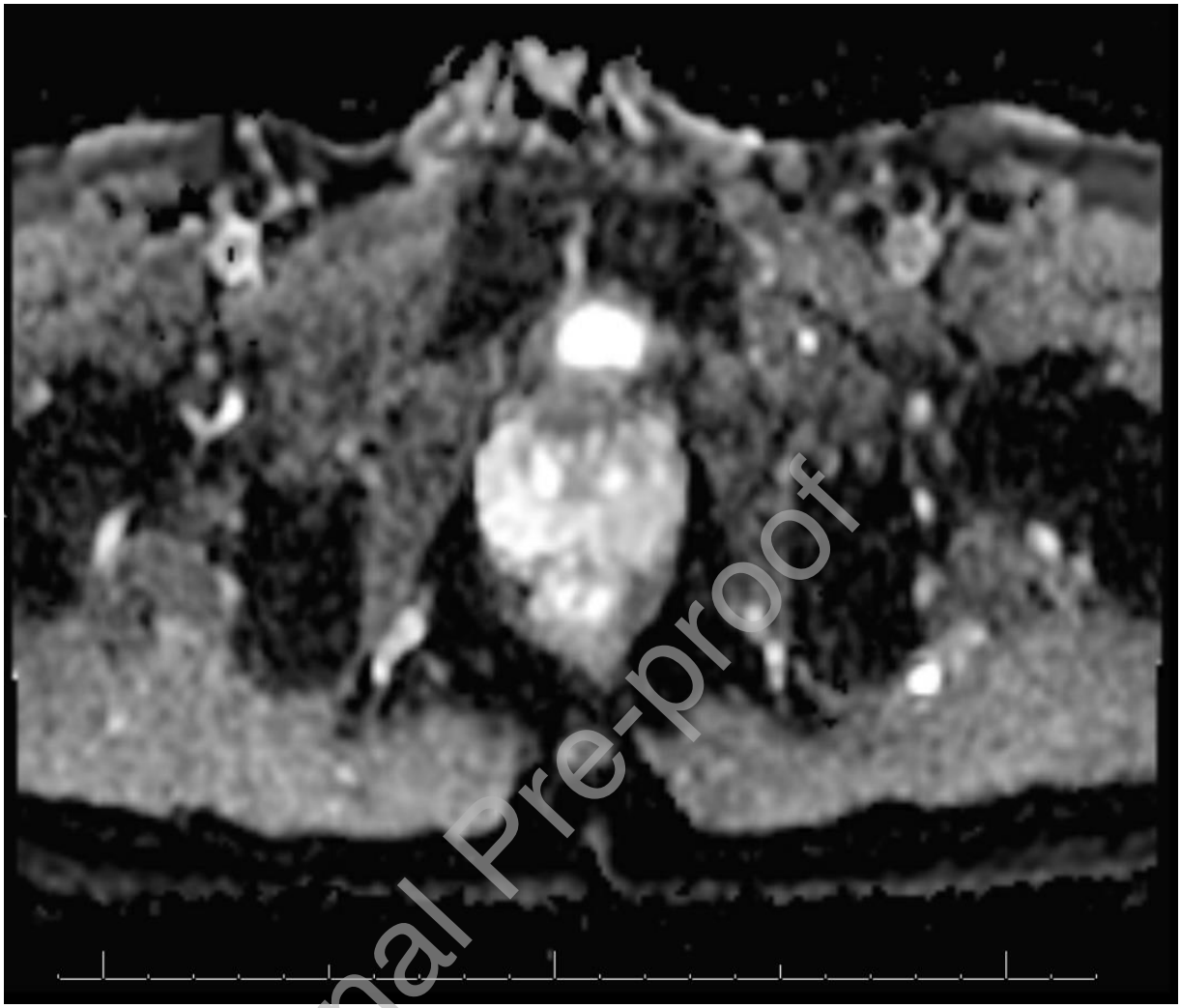

Figure 2. Diffusion restriction image showing corroboration of lesion seen on T2 sequences in the anterior gland

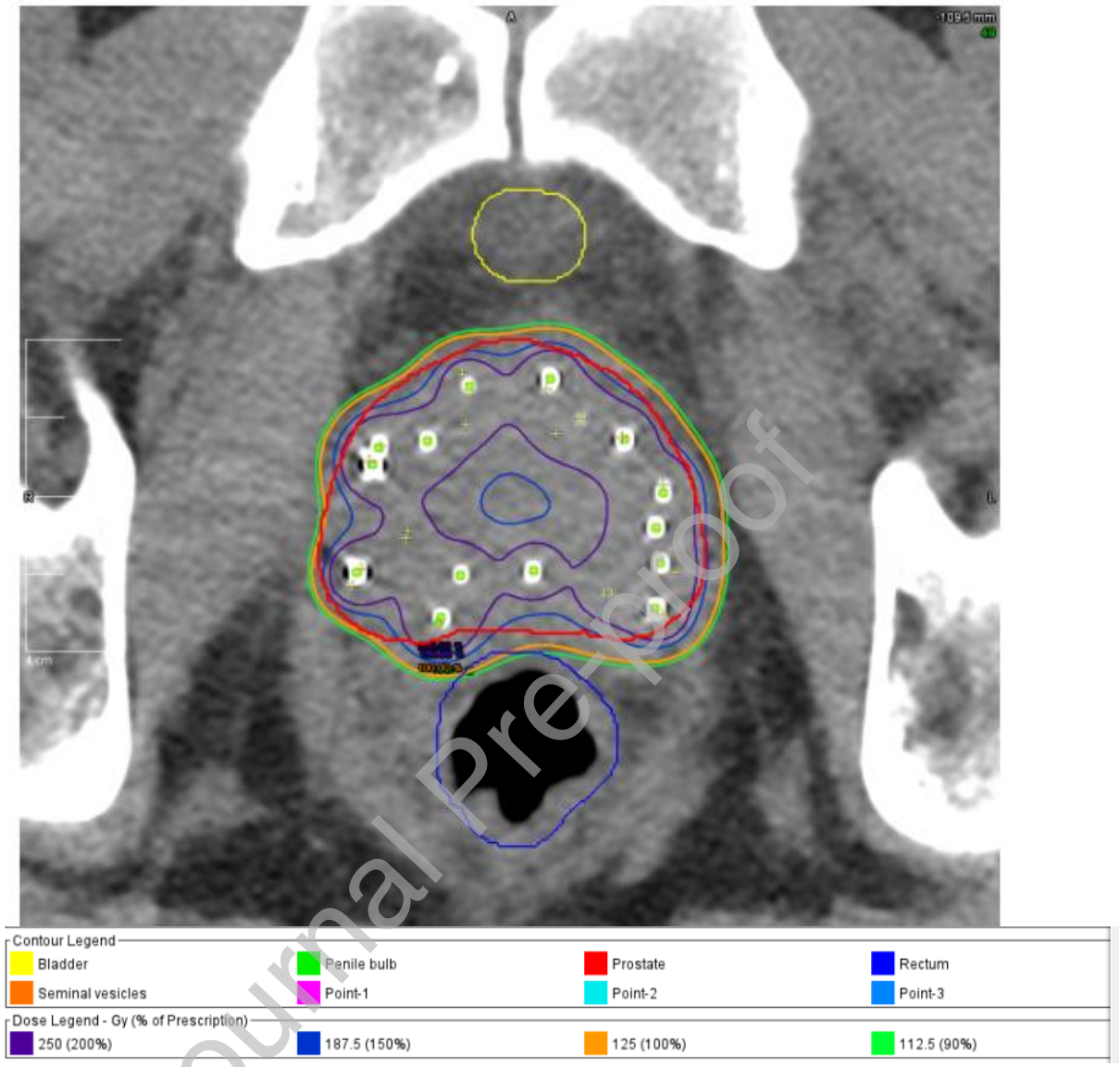


Figure 3: Representative cross-section showing seed placement and isodose lines after prostate brachytherapy

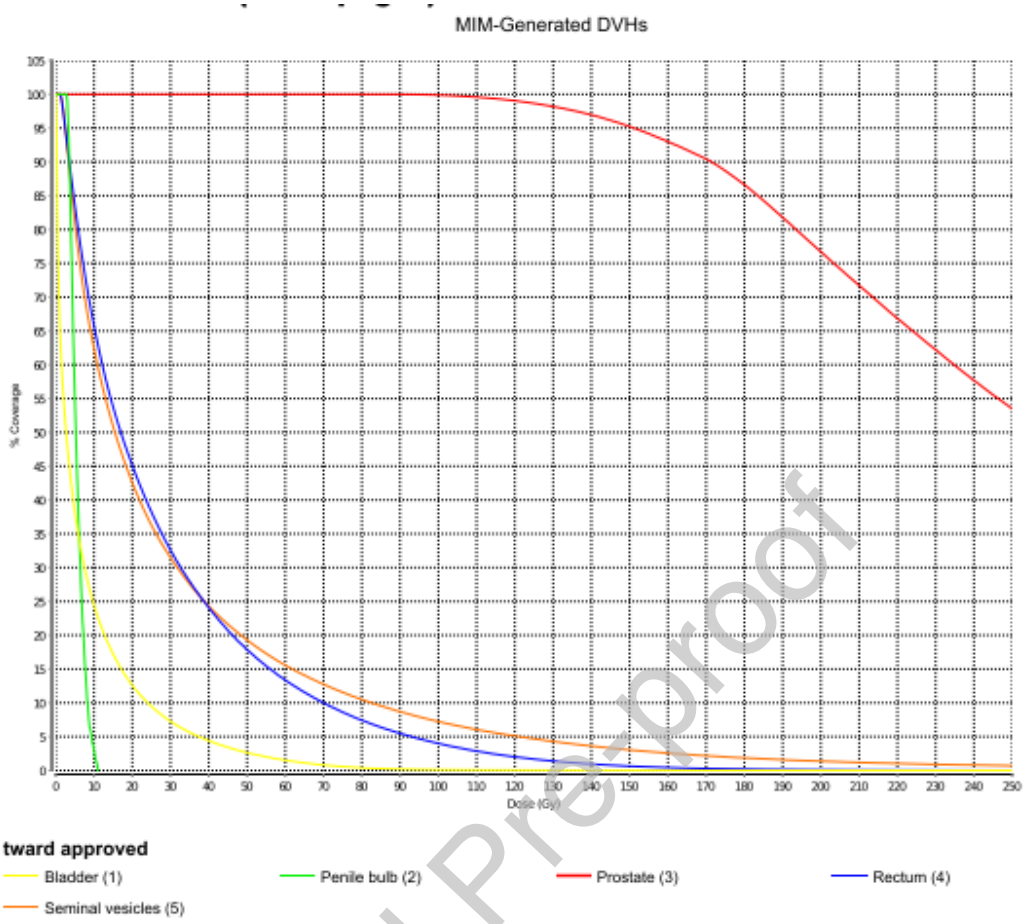


Figure 4: Dose Volume Histogram parameters at Day 1 post-implant dosimetry

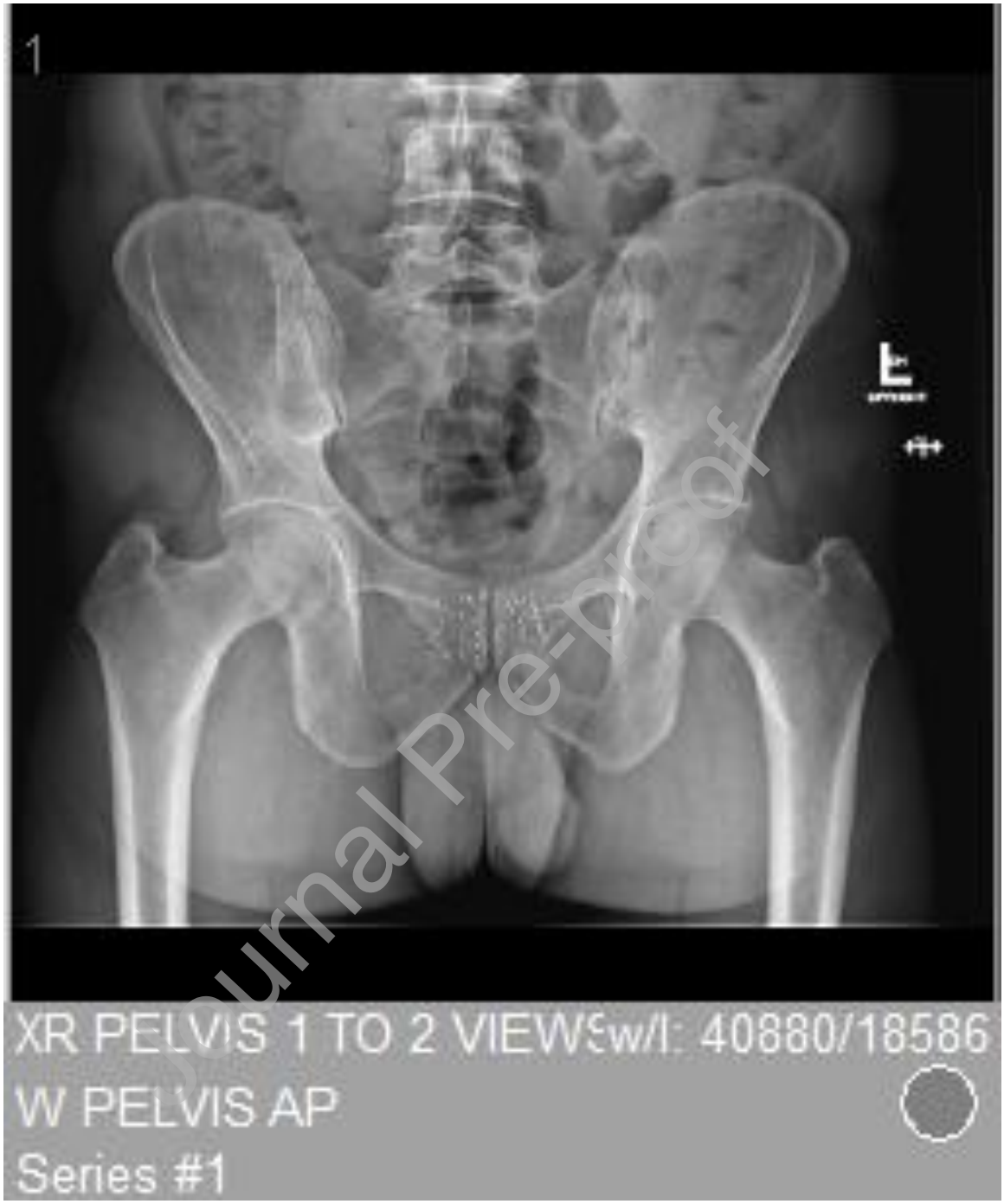


Figure 5: AP projection of Palladium 103 brachytherapy seeds in the region of the prostate gland

Function Scores. Treated in May 2021

| | Date | AUA | SHIM | RFAS | EPIC-CP Incontinence | EPIC-CP Irritative | EPIC-CP Rectal | EPIC-CP Sexual | EPIC-CP Hormonal |
|---|---|---|---|---|---|---|---|---|---|
| Pretreatment | 12/26/2020 | 19 | 25 | N/A | | | | | |
| | 4/28/2021 | 17 | 25 | N/A | | | | | |
| 6 months post | 11/11/2021 | 15 | 25 | 4 | 2 | 4 | 1 | 0 | 0 |
| 1 year post | 05/26/2022 | 18 | 25 | 3 | 0 | 4 | 0 | 0 | 0 |

Table 1: Health-related quality of life indices. AUA: AUA Symptom Index. SHIM: Sexual health inventory in men. RFAS: Rectal Function Assessment scale. EPIC-CP: Expanded Prostate Index Composite- Clinical Practice