Vascular Targeted Photodynamic Therapy for Localized Prostate Cancer

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Survival for men diagnosed with prostate cancer directly depends on the stage and grade of the disease at diagnosis. Prostate cancer screening has greatly increased the ability to diagnose small and low-grade cancers that are amenable to cure. However, widespread prostate-specific antigen screening exposes many men with low-risk cancers to unnecessary complications associated with treatment for localized disease without any survival advantage. One challenge for urological surgeons is to develop effective treatment options for low-risk disease that are associated with fewer complications. Minimally invasive ablative treatments for localized prostate cancer are under development and may represent a preferred option for men with low-risk disease who want to balance the risks and benefits of treatment. Vascular targeted photodynamic therapy (VTP) is a novel technique that is being developed for treating prostate cancer. Recent advances in photodynamic therapy have led to the development of photosynthesizers that are retained by the vascular system, which provides the opportunity to selectively ablate the prostate with minimal collateral damage to other structures. The rapid clearance of these new agents negates the need to avoid exposure to sunlight for long periods. Presented herein are the rationale and preliminary data for VTP for localized prostate cancer.
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Prostate cancer represents the second most common cause of cancer-related deaths in American men; it is estimated that 27,000 men in the United States died from the disease in 2007.[1] Survival for men with prostate cancer directly depends on the stage and grade of the disease at the time of diagnosis.[2] These sobering mortality statistics and the more favorable prognosis associated with early detection provide the primary justification for prostate cancer screening,

which is performed by measuring the level of serum prostate-specific antigen (PSA) and conducting a digital rectal examination (DRE). It is estimated that 50% of men over the age of 50 years are screened annually for prostate cancer.[3]

Despite widespread acceptance, prostate cancer screening is debated,[4,5] and recommendations for prostate cancer screening are inconsistent. Screening protagonists emphasize that radical prostatectomy increases prostate cancer survival in men with localized disease,[6] and that the recently observed progressive and significant decline in prostate cancer mortality rates is the direct result of PSA screening and aggressive intervention.[7] Screening antagonists emphasize the indolent natural history of most prostate cancers detected by screening,[8] and that the vast majority of men who are treated for prostate cancer do not recognize any survival advantage from early detection and are simply left suffering the ravages of treatment.[9]

Both sides of the screening debate have valid arguments. In the absence of widespread screening, many men are denied an opportunity to cure their disease. These men will experience the otherwise preventable consequences of disease progression, which include the development of androgen-insensitive disease[10] and death. However, widespread screening exposes many men to unnecessary complications associated with treatment for localized disease. The challenges are to identify and treat only those cancers that have the biological potential to cause serious and preventable consequences, or to develop treatment options that are associated with fewer complications.

Assessing the Extent of Prostate Cancer

An elevated serum PSA level and/or an abnormal DRE identify a cohort of men who have a higher risk of prostate cancer detected on biopsy. The majority of prostate cancers are diagnosed in men with an elevated PSA level and normal DRE.[11] Because PSA is produced by both benign and malignant prostatic elements, this screening test has inherent limitations due to its lack of sensitivity and specificity for prostate cancer detection.

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It is well established that the risk of detecting prostate cancer is directly related to the level of serum PSA. There is no true normal serum PSA level because a level between 1.0 and 2.0 ng/mL is associated with a 10% risk of prostate cancer on prostate biopsy.[12] Those who advocate lowering the threshold serum PSA level for recommending biopsy argue that the prostate cancer detection rate will be significantly increased while simultaneously increasing the proportion of men diagnosed with pathologically organ-confined tumors.[13] The concern is that lowering the threshold serum PSA level for recommending prostate biopsy increases the detection of smaller and less aggressive cancers that may not represent a threat to the older host.

The increasing life expectancy of men poses new challenges for therapeutic interventions.

There are several characteristics of prostate cancer captured by prostate biopsy, including Gleason score, tumor volume, and perineural invasion, that predict both pathological stage and biochemical recurrence following radical prostatectomy.[14-16] These tumor characteristics, when combined with serum PSA level and clinical stage, have been utilized to construct nomograms that predict individual risk of extracapsular extension and biochemical recurrence following radical prostatectomy.[17] Thus, it would seem logical to use these predictors of pathological stage and biochemical recurrence to identify individuals with low-risk disease who are unlikely to benefit from curative intervention. It is also important to recognize that the risk of disease is dependent not only on the extent and aggressiveness of the prostate cancer, but also on the life expectancy of the host. A small, low-grade cancer may pose a threat to a 50-year-old man, whereas a large cancer with a Gleason score of 7 and extracapsular extension may pose little threat to a 75-year-old man who has significant comorbidities. Owing to the increased longevity of the elder population (ie, of the baby boomers), it is no longer reasonable to assume that all 75-year-old men with prostate cancer do not benefit from curative treatments. The increasing life expectancy of men poses new challenges for therapeutic interventions.

The risk of prostate cancer is categorized as low, intermediate, and high based on clinical stage, serum PSA level, and Gleason score.[18] Low-risk disease is defined by clinical stage T1c or T2a disease, a serum PSA level less than 10 ng/mL, and a Gleason score of 6. The majority of these men have organ-confined disease and, therefore, have very favorable outcomes following radical prostatectomy[18] or

radiation therapy.[19] It is unknown what proportion of these men would have experienced a favorable outcome if untreated.

Is Active Surveillance a Reasonable Option for Low-Risk, Localized Prostate Cancer?

Epstein and colleagues[20] examined biopsy and radical prostatectomy specimens to elucidate biopsy tumor characteristics that would reliably predict the presence of low-risk disease. The investigators observed that men with Gleason score 6 cancers involving less than 3 biopsy cores with a PSA density less than 0.15 have a 70% probability of clinically insignificant disease, defined as a tumor volume in the surgical specimen less than 0.5 cm^3. It is important to note that this tumor volume cutoff value was arbitrarily defined as clinically insignificant. Few would argue that disease of this low volume would threaten the life of a man with only a 10-year life expectancy. It is less certain that this same small tumor volume would be clinically insignificant in a 50-year-old man with a 30-year life expectancy.

Based on these early observations, Carter and associates[21] prospectively followed men designated as having low-risk cancers by the Epstein criteria with interval serum PSA levels and scheduled repeat prostate biopsies to capture disease progression. With up to 5 years of follow-up data, there have been no prostate-cancer mortalities. These short-term and preliminary observations have been used to justify active surveillance in men with low-risk disease and short life expectancies.[22]

Klotz[23] extended the indications for active surveillance to include all men with low-risk disease as defined by the D'Amico criteria. In this cohort of men with a strong commitment to active surveillance, 34% ultimately received curative intervention due to progression or patient dissatisfaction with following an active surveillance regimen.

The major concern of active surveillance in men with low-risk, localized disease as defined by Carter and colleagues or Klotz is that a significant subset of these men harbors aggressive disease. Several investigators report significant understaging of low-risk disease based on prostate biopsy.[24,25] We recently examined a cohort of 771 consecutive men with low-risk disease based upon prostate biopsy characteristics who underwent open radical retropubic prostatectomy at the time of diagnosis (H. Lepor, unpublished data, October 2008). All of these men are considered candidates for active surveillance according to the Klotz recommendation. Of these men, 47% were found to have disease with a Gleason score of 7, 13% had a primary pattern with a Gleason score of 4, 11% exhibited extracapsular extension, and 30% had tumors occupying over 20% of the volume of the prostate. Seventeen percent of men with low-risk disease developed biochemical recurrence despite undergoing radical prostatectomy. These findings collectively demonstrate the inability to reliably identify candidates with low-risk disease and suggest that many individuals with long life expectancies may be jeopardized by delayed treatment.

Rationale for Minimally Invasive Treatments for Clinically Localized Prostate Cancer

The overwhelming majority of men diagnosed with low-risk prostate cancer elect curative intervention.[22] Only about 10% of men diagnosed with low-grade disease elect active surveillance as their initial treatment. The fact that a significant proportion of men initially selecting active surveillance ultimately pursue curative intervention because of disease progression or the psychological burden of potentially compromising their survival suggests that this strategy is not a long-term, viable alternative in many cases.[23] In retrospect, about 50% of men diagnosed with low-risk disease who ultimately undergo radical prostatectomy or radiation therapy truly have minimal disease and may be exposed to the risks of treatment without a likely survival advantage (H. Lepor, unpublished data, October 2008). Clearly, the risks and benefits of active surveillance versus curative treatment options are heavily dependent on life expectancy.

Minimally invasive ablative treatments for localized prostate cancer are under development and may represent a preferred option for men who want to balance the risks and benefits of treatment versus active surveillance. The ultimate role of minimally invasive ablative treatments will depend on whether the disease can be reliably ablated without significant procedural or quality-of-life complications.[24,25] There are a myriad of potential complications associated with radical prostatectomy and radiation therapy. With the exception of erectile dysfunction, clinically significant complications are relatively rare following established treatment options.[26-28] Therefore, the primary opportunity for minimally invasive ablative treatment is to reduce trauma to the cavernous nerves, resulting in less erectile dysfunction. Because of

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the proximity of the neurovascular bundle to the prostate, it is unlikely that minimally invasive ablative treatment will totally ablate the gland without some collateral injury to the nerves mediating erectile function. However, image-guided, real-time, minimally invasive treatment holds the promise of ablating virtually the entire gland with less damage to the neurovascular bundle than nerve-sparing radical prostatectomy and radiation therapy.

There are 2 fundamental advantages of minimally invasive ablative treatment over radical prostatectomy and radiation therapy that are relevant to the management of low-risk disease. Unlike radical prostatectomy, the entire prostate does not have to be ablated. This provides the opportunity to offer focal therapy targeting a dominant lesion or hemi-ablation that targets the involved side of the gland. VTP may adequately spare a sufficient component of the neurovascular bundle so that potency is preserved. The future challenge is to employ advances in biopsy techniques and imaging to more reliably pinpoint the site(s) and aggressiveness of the disease with the intent of identifying those patients with low-volume disease who do not require total eradication of the gland to reduce the lifetime risk from the disease. Another advantage of minimally invasive ablative treatment is the opportunity for retreatment. Unlike radiation therapy, primary and salvage strategies that refreeze, reheat, or revaporize the gland will likely be associated with acceptable risks. With the ablation of virtually all the benign tissue, posttreatment serum PSA levels will likely emerge as a very accurate measure of clinically significant residual disease that would trigger the indication for repeat treatment.

Because the majority of prostate cancers currently diagnosed are low risk, minimally invasive ablative therapy targeting this cohort of men will likely play a significant role in the management of prostate cancer. Although many experts suggest that minimally invasive ablative therapy will ultimately be offered to men with low-risk disease who do not require treatment, they must reconcile that the majority of cases in large, prospective series of radical prostatectomy patients are composed of men with low-risk disease[26,29-31] who are the candidates for minimally invasive ablative treatment.

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Status of Minimally Invasive Ablative Treatments for Localized Prostate Cancer

Beginning in the 1970s, the US Food and Drug Administration mandated that new medical devices undergo a formal and rigorous approval process before gaining access to the US market. This process requires demonstration of both safety and effectiveness. Treatments that were already on the market were exempt under a 510(k) regulation that required demonstration of safety only.

Because cryotherapy devices were on the US market prior to the 1970s, registration studies were not required in order to market second- and third-generation prostate cryotherapy devices for general use and not specifically for prostate cancer. However, because of the significant morbidity associated with this ablative technology, cryotherapy has not gained widespread acceptance for the total ablation of the prostate for localized disease.

Two different high-intensity focused ultrasound devices are currently under investigation in the United States.[32-34] The technology is approved in many countries worldwide.

Photodynamic therapy (PDT) is a novel treatment for localized prostate cancer that is under investigation, but has not yet received marketing approval in any country.

Development of Photodynamic Therapy for Localized Prostate Cancer

The optimal photodynamic ablative therapy for prostate cancer requires the development of an agent with photosensitizing properties that is selectively taken up by prostate cancer cells. Energy-delivering probes are also required to deliver the appropriate wavelength of light energy to the photosensitizer taken up by prostate cancer cells. Ideally, the photosensitizer is rapidly cleared by the body to minimize posttreatment inconvenience.

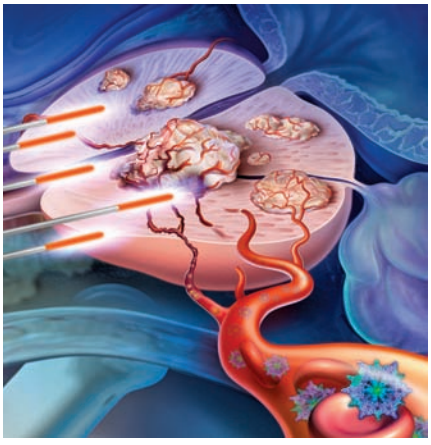
In urology, PDT was initially developed for the treatment of superficial bladder cancer[35]; the bladder appeared to be ideally suited for PDT because light could be directly delivered into the bladder lumen under cystoscopic guidance. The goal was ablation of both the superficial visible tumor and foci of carcinoma in situ that were not readily visible. In early, investigational bladder cancer trials, photofrin was the photosensitizer of choice.

There were several limitations in this early experience with PDT. The photosensitizer was only modestly selective for urothelial cancer cells and, therefore, many foci of carcinoma in situ were undetected. It was also

difficult to control the penetration depth of the light energy, resulting in bladder perforations. Finally, the prolonged photosensitizer half-life mandated that the patient avoid exposure to sunlight for 6 weeks. 5-Aminolevulinic acid (5-ALA) is a precursor that initiates the endogenous production of a photoporphyrin sensitizing agent. Recently, 5-ALA–based PDT was shown to be preferentially sequestered in superficial bladder tumor cells.

In many ways the prostate is also well suited for PDT. Because the prostate does not typically serve a vital function in most men who have prostate cancer, selective uptake of the photosensitizer by cancer cells is not necessary because there are no significant consequences associated with destroying normal prostate tissue. At the same time, it is imperative to avoid collateral tissue necrosis to adjacent structures, including the cavernous nerves, bladder, rectum, and urinary sphincter mechanism. Importantly, the therapeutic targets can be either the cellular or vascular compartments of the prostate.

Figure 1. *During photodynamic therapy (PDT), a photosensitizing agent is injected intravenously and is distributed throughout the body. Small energy-delivering probes deliver the appropriate wavelength of light energy. To treat localized prostate cancer, these probes could be positioned to deliver PDT to either a portion of or to the entire gland.*



Tremendous advances have been made in developing PDT delivery systems that are targeted to the vascular bed. The target tissue selection is a key factor in the treatment outcome because it introduces an element of biological moderation. A photosensitizing agent is injected intravenously and is distributed throughout the body (Figure 1). Using modern imaging technology and borrowing needle placement grids developed for brachytherapy, small energy-delivering probes could be positioned in the prostate to deliver PDT to either a portion of or to the entire gland.

Using modern imaging technology and borrowing needle placement grids developed for brachytherapy, small energy-delivering probes could be positioned in the prostate to deliver photodynamic therapy to either a portion of or to the entire gland.

The first experience with PDT of the prostate was reported by Windahl and colleagues[36] in 1990. The investigators utilized hematoporphyrin or polyporphyrin (photofrin-like compounds) as the photosensitizer in 2 cases of localized prostate cancer. Since this initial experience, 3 other groups have reported small-scale experiments using PDT for the treatment of prostate cancer.[37-39] In the more recent studies, PDT was offered as salvage therapy after failed external beam radiotherapy (EBRT).

A novel PDT developed by the Weizmann Institute (Rehovot, Israel) with support from STEBA Biotech N. V. (The Hague, Netherlands) is currently under investigation in many centers worldwide for treatment of both localized disease and salvage therapy following failed EBRT. WST-09 (Tookad®; STEBA Biotech N. V.), the prototype photosensitizer, is a palladium bacteriopheophorbide molecule that was synthesized from the native bacteriochlorophyll a molecule,[40,41] produced in dark-growing bacteria under aerobic conditions. Recently, a water soluble derivative of palladium bacteriopheophorbide, termed *WST-11* (Stakel®), was prepared by the same group[42] and developed for pharmaceutical application by STEBA Biotech N. V.[43] There are many features of both photosensitizers that render them optimal for treatment of prostate cancer (Table 1).[44] The 2 compounds stay only in the circulation until clearance either in micelles (WST-09) or as a noncovalent complex with human serum albumin (WST-11). Hence, the radical oxygen species generated by this sensitizer are strictly limited to the vascular bed; this therapeutic approach is termed *vascular targeted photodynamic therapy* (VTP). Because the photosensitizer is confined to the vasculature, the mechanism for cell death is primarily attributed to vascular occlusion and other processes that originate in a vascular oxidative stress. The light source is delivered via optical fibers positioned under ultrasound guidance using a standard brachytherapy stabilizing frame and template. Another major advantage of WST-09 and WST-11 is their rapid clearance first from the circulation and then from the liver. Under these conditions, patients are not required to avoid sunlight and other forms of photonic radiation shortly after treatment. WST-11 appears to have a significantly larger therapeutic index and should be far easier to use in the context of VTP, which requires water soluble circulating agents. The clinical studies reported to date in the literature have utilized WST-09.

Table 1
Advantages of Photosensitizers WST-09 and WST-11

Advantage	Implication
Water soluble (WST-11)	Ease of preparation/administration
	Avoids complications due to liposomal formulations
Confined to circulation until clearance	Selective tissue destruction
Cleared rapidly from circulation and liver	Avoidance of sunlight exposure reduced to hours
Connective tissue more resistant to VTP effect	Optimize quality-of-life outcomes Allows other treatments if fails
Activated by light at 753-7 nm (WST-011) and 763 nm (WST-09)	Deep penetration into tissue Allows for large volume of destruction in a short treatment time

VTP, vascular targeted photodynamic therapy.

There is preliminary evidence that connective tissue may be more resistant to VTP, and that it reflects back into the gland a significant amount of the incident light generated during VTP with WST-09. If this proves true, the neurovascular bundle adjacent and outside of the prostate capsule may exhibit some selective resistance to damage when the goal is to achieve total gland ablation.

WST-09 and WST-11 are activated by light at 763 nm and 753-7 nm, respectively. Because these wavelengths of light are at the near infra-red, it allows for a deeper light penetration into tissues that is desirable for ablation of a large tissue volume. The light is delivered from diode lasers through optical fibers positioned under ultrasound guidance using a standard brachytherapy stabilizing frame and template.

Measuring posttreatment PSA is the optimal method for determining if the prostate has been totally excised or ablated and that there is no evidence of residual local or systemic disease. For partial ablation procedures, contrast-enhanced magnetic resonance imaging (MRI) represents a potential approach for monitoring technique success,[45] because any viable residual prostate tissue would be enhanced and the residual untargeted prostate tissue would produce PSA.

Clinical Experience With VTP Using WST-09 for Localized Prostate Cancer

There are 2 published studies examining the safety and effectiveness of VTP using WST-09 in the literature.[46,47]

Twenty-four men with biopsy-proven recurrent prostate cancer following definitive radiotherapy were enrolled in a phase I/II study at different centers in Canada.[46] Enrollment criteria included life expectancy exceeding 5 years, no evidence of regional or systemic disease on abdominopelvic computerized tomography, PSA less than 20 ng/mL, prostate volume less than 50 cm^3, and Gleason score greater than 6. The study included a drug dose escalation arm. Once drug safety was demonstrated, a second arm examined light dose escalation.

VTP was performed under general anesthesia in the lithotomy position. A standard brachytherapy stabilizing frame with the template modified with 13-gauge holes was used to place transparent, closed-end catheters in the prostate under ultrasonic guidance. Optical fibers that included a light source and probes for light dosimetry were inserted into these catheters. The source fibers were connected to a 763-nm light diode. Light exposure to the rectum was limited via a hydrodissection procedure.

Treatment response was measured by contrast-enhanced MRI on day 7 and at 6 months, prostate biopsy at 6 months, and serum PSA measurements at 1, 2, 3, and 6 months. Potency, continence, voiding symptoms, and rectal symptoms were captured using validated questionnaires.

At the maximal evaluated dose of 2 mg/kg, there were no significant drug-related adverse reactions. Several subjects experienced transient hypotension soon after infusion of the WST-09 solution that promptly responded to fluids and pressors.

Measurements taken 3 to 5 mm from the source fibers did not show any significant changes in tissue temperature. The lesion diameter ranged between 5 and 10 mm. There were no injuries to the rectum or urethra, even at the maximum light dose.

In areas that have become avascular due to WST-09 VTP as observed 1 month after treatment on contrast-enhanced MRI, there were no viable tumors as demonstrated by targeted biopsies. In all biopsies obtained from outside the avascular zones, residual cancer was detected.

Urinary, bowel, and rectal function were not significantly different between baseline and posttreatment assessment at 6 months.

A phase II escalating light dose study using 2 mg/kg WST-09 VTP that enrolled 28 men with recurrent prostate cancer following failed EBRT was recently published.[47] The objective of this study was to treat the entire prostate. The inclusion criteria and outcome parameters were similar to those of the phase I/II study. The light dose was escalated based on the data generated in real time correlating volume of tissue devascularized as a function of light dose, which was ascertained on day 7 via contrast-enhanced MRI. The infusion period lasted 20 minutes and light delivery lasted 30 minutes. Analysis of treatment results was based on dose received by the prostate rather than the energy delivered by the fibers.

A large variation in efficacy was observed in the response captured by residual cancer on prostate biopsy and MRI avascular effect. Greater light doses were administered to patients enrolled as the study progressed. In general, increasing light doses resulted in greater avascular effect. Of the 13 subjects who had a minimum light dose received by 90% of the prostate volume exceeding 23 J/cm^3, 8 experienced a complete response that included negative biopsies at 24 months. All subjects with an MRI response of greater than 60% devascularized prostate exhibited a complete response. This rate is similar to that observed with cryotherapy,[46] which is emerging as an accepted salvage treatment for EBRT failures.

Overall, 10 subjects had some devascularization of the rectum noted on contrast-enhanced MRI at day 7. In the majority of these cases, there were no clinical consequences secondary to rectal ischemia. Of the 2 subjects who developed rectourethral fistulas, 1 healed spontaneously. The case with a persistent fistula developed hemorrhagic proctitis following EBRT that may have been a predisposing factor for fistula formation. As previously observed, there were no clinically significant adverse effects on erectile or urinary function. Although experience to date is small, the advantage of WST-09 VTP over cryotherapy appears to be fewer adverse reactions.

There is little information on the light dose dependency of WST-09 VTP in the nonirradiated prostate. Phase I and II studies are required to define treatment parameters in this clinical setting as WST-09 VTP is further investigated in men with low-risk, localized prostate cancer. The preliminary observation indicating a differential devascularization effect between neural and epithelial tissue using WST-09 VTP may be exploited to achieve complete gland ablation without collateral damage to the neurovascular bundle, minimizing erectile dysfunction.

Conclusions

There are definite limitations for active surveillance and the curative treatment options that are currently available for managing low-risk, clinically localized prostate cancer. Because most prostate cancers are low risk and clinically localized, the majority of newly diagnosed men are confronted with how best to manage their disease. If minimally invasive ablative treatment options reliably cure or control low-risk disease, men will likely select this pathway over active surveillance or radical prostatectomy and radiation therapy.

WST-09 VTP represents a novel strategy for achieving the goals of a minimally invasive treatment. The preliminary results are quite encouraging, but there is a long way to go before WST-09 VTP and other minimally invasive ablative treatment can be offered with the confidence that survival is not compromised and quality of life is enhanced. ■

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Main Points

- The major concern of active surveillance in men with low-risk, localized disease is that a significant subset of these men harbors aggressive disease. Many individuals with long life expectancies may be jeopardized by delayed treatment.
- The primary opportunity for minimally invasive ablative treatment is to reduce trauma to the cavernous nerves, resulting in less erectile dysfunction. Vascular targeted photodynamic therapy (VTP) may adequately spare a sufficient component of the neurovascular bundle so that potency is preserved.
- There is preliminary evidence that connective tissue may be more resistant to VTP, and that it reflects back into the gland a significant amount of the incident light generated during VTP with WST-09 and WST-11. If this proves true, the neurovascular bundle adjacent and outside of the prostate capsule may exhibit some selective resistance to damage when the goal is to achieve total gland ablation.
- If minimally invasive ablative treatment options reliably cure or control low-risk disease, men will likely select this pathway over active surveillance or radical prostatectomy and radiation therapy.

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