Research and Reports in Urology

Dovepress
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REVIEW

Patient Reported Outcomes and Treatment-Associated Complications as a Consideration in Selecting Localized Prostate Cancer Management

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Abstract: Localized prostate cancer (PCa) remains the most common noncutaneous cancer in men, with numerous management options tailored to individual patient needs. This review examines the role of patient-reported outcomes (PROs) in guiding the management of localized PCa, focusing on the impact of various treatments on long-term quality of life. Standard therapies, including radical prostatectomy, radiotherapy, and active surveillance, are discussed alongside emerging focal therapies. Each treatment modality presents distinct risks, notably urinary incontinence, erectile dysfunction, bowel issues, and cancer recurrence. Understanding these adverse effects in terms of PROs is critical for patients and healthcare providers to engage in shared decision-making, enabling personalized treatment plans based on clinical outcomes and patient values. The incorporation of PROs into treatment selection emphasizes the significance of balancing oncologic control with functional outcomes, such as sexual, bowel, and urinary health. The importance of patient counseling is underscored, ensuring patients are fully informed about potential complications and long-term implications. This review advocates for personalized, evidence-based management strategies that align therapeutic decisions with individual patient preferences, optimizing both survival and quality of life. Enhanced communication between patients and clinicians, informed by PROs, is critical for minimizing decisional regret and maximizing satisfaction in the management of localized PCa.

Keywords: prostate cancer, treatment, radical prostatectomy, radiotherapy, focal therapy, patient reported outcomes, complications

Introduction

Prostate cancer (PCa) is the leading noncutaneous cancer diagnosed in American men and accounts for 29% of all cancer incidences in men.[1–3] 1 in 8 US men develop the disease over their lifetime and are typically affected between the ages of 45 and 60.[2–4] Prostate biopsy, prostate-specific antigen (PSA) testing, digital rectal examination, magnetic resonance imaging (MRI), and routine health screening all aid in the detection and diagnosis of PCa. Despite the high incidence rate, the 5-year relative survival is 97% for all stages of the disease combined.[2] The 10-year survival rate in men depends on the risk category, ranging from 3–18%.[1,5] Localized PCa is defined as prostatic malignancy contained within the capsule of the prostate without evidence of local or distant metastasis.

Widespread PSA screening and treatment advancements have led to a significant decline of 53% in PCa mortality since its peak in 1993.[3,6] Consequently, relatively few PCa patients die from the disease itself.[6] In the US, the risk of dying from prostate cancer is approximately 2.6%.[6] In most cases, the risk of death for PCa is more often superseded by the risks from other causes such as medical comorbidities and/or age.[1,5,7,8] However, the goal of prostate cancer treatment for some patients is to avoid the morbidity associated with metastatic burden as metastasis occurs in >50% of men with localized disease.

Received: 14 September 2024
Accepted: 9 April 2025
Published: 12 June 2025

For patients diagnosed with localized cancer, several management options are available. Standard therapeutic options consist of active surveillance and whole gland treatment including radiotherapy and radical prostatectomy. Furthermore, new alternatives such as focal therapy are emerging treatment options. Each approach carries subsequent risk of complications that may impact various physiologic functioning and overall quality of life. Specific outcomes may also vary according to initial patient and tumor characteristics. As a result, counseling patients with localized prostate cancer regarding treatment options has become an increasingly complex process.[9] This is where patient reported outcomes (PROs) becomes vitally important. PROs involve standardized questionnaire and/or documented symptoms after a treatment that can be collected and analyzed for downstream determination of treatment-associated complications and quality of life. In terms of treatment decision making, informing a patient on PROs can assist them by providing a complete informed consent. This manuscript reviewers specific PROs and treatment-associated complications for localized prostate cancer.

Cancer staging, initial patient characteristics, life expectancy, and patient preferences are all involved in guiding treatment selection.[1,9] Shared decision-making between patient and provider allows patients to make autonomous, informed decisions about their health following PCa diagnosis. Therefore, proper patient and physician understanding of the potential risks and expected outcomes of available treatments is necessary. In this review, we will discuss the available PCa management options, complications, and patient-reported outcomes.

Mainstay Treatments of Localized Prostate Cancer

Prostatectomy

Prostatectomy is a common surgical treatment for clinically localized PCa that removes the prostate.[10] A radical prostatectomy (RP) involves the removal of both the prostate and seminal vesicles. For nerve sparing operations, care is taken to preserve the cavernous nerves present bilaterally in the neurovascular bundles that run along the prostatic capsule. There are multiple approaches to RPs that can be chosen by availability, patient preference, patient outcomes, or surgeon expertise.

Surgical management of PCa began in 1904 with the first radical perineal prostatectomy.[11] In 1945, the retropubic approach was developed and provided a more familiar anatomy for urologists. It also provided access for simultaneous dissection of pelvic lymph nodes for staging.[10] Further innovation in open radical prostatectomies (ORP) led to improvement in nerve-sparing and operative speed with ORPs still being a viable treatment option today for the selected patient and is largely reserved for those with extensive abdominal adhesions.[12]

The development of the laparoscopic prostatectomy (LRP), in 1991, was the next major innovation in surgical prostatectomy.[13] LRP provided patients surgery with complication rates comparable to those of ORP with the benefits of minimally invasive surgeries.[14] Minimally invasive surgeries bypass painful flank or abdominal incisions, shortening the length of a hospital stay, and allow for a quicker return to activities.[14] However, LRPs require a steeper learning curve with less degree of freedom for suturing and dissection coupled with decreased visibility.[13] The difficulties attributed to LRP led to a lack of adoption by many surgeons and the continued use of ORP. This changed with the advent of the robotic-assisted radical prostatectomy (RARP).[15] The first RARP was done in 2000 and improves on many of its predecessor's, LRP, shortcomings. RARP provides a 3D operating view, reduced operator learning curve, and complete control over all instruments and camera.[13,16] Some studies have shown further reduced bleeding, need for blood transfusions, and recovery time.[16] However, when comparing potency and continence between the RARP and ORP there is no definitive clinical significance.[13,17,18]

Today, definitive therapy can be determined by a patient's risk stratification as outlined on the NCCN guidelines:

- Very low-risk clinically localized PCa, are preferred to be managed with active surveillance.
- Low-risk PCa and a life expectancy greater than 10 years, active surveillance is the preferred management option.
- Intermediate-risk PCa are divided into favorable and unfavorable subsets and suggested definitive treatment. Active surveillance is an option for the favorable intermediate-risk disease.
- High-risk, and very-high risk PCA are suggested definitive therapy.[19]

In both intermediate risk patients who elect for definitive therapy and higher-risk patients for whom it is recommended, the choice among definitive therapies is again guided by the specific benefits and drawbacks of each treatment, tailored to the patient's unique circumstances. For example, a requirement to do a RP is the tumor be free from any surrounding structures and that no distant metastases are present.[6] Furthermore, RPs are also relatively contraindicated in patients with higher medical operative risks and neurogenic bladders.[20,21] Certain advantages of RP include effective long-term cancer control, precise prognosis based on pathologic features in specimens, and pelvic lymph node accessibility through the same incision.[21] Certain disadvantages of RP include significant risk of erectile dysfunction, operative morbidity, and urinary incontinence.[21] These factors highlight some variables to consider when creating an individualized treatment plan to maximize therapeutic benefits while minimizing potential risks.

Radiation

Radiation therapy is used to manage prostate cancer by delivering a lethal amount of radiation to areas of cancerous prostatic tissue while preserving the surrounding normal tissue.[6] Radiotherapy for prostate cancer includes external beam radiation therapy (EBRT) and brachytherapy (BT). EBRT is the most common type of radiotherapy and uses focused X-ray beams to target specific cancerous areas mapped by CT and MRI scans. Treatment fields can also include the seminal vesicles and/or regional lymph nodes when direct evidence of tumor involvement or the likelihood of malignancy is calculated to be 15% or greater.[6,22,23] BT involves the surgical implantation of tiny radioactive seeds within the prostate.[6] The radiation emitted by these seeds induces apoptosis of cancerous cells without exposing surrounding healthy organs to high levels of radiation.[24,25]

For patients receiving EBRT, conformal techniques, including intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT), are considered the standard of care. Image-guided intensity-modulated radiation therapy (IG-IMRT) involves the use of multiple radiation beams which intersect within the target volume with energy deposition maximized within the tumor.[26] The beam intensity can be adjusted according to the specific area being targeted, allowing for precise irradiation of the tumor with minimal exposure to surrounding normal tissues.[24] The prostate is localized daily via implanted fiducial markers and diagnostic quality x-rays, allowing for the margins to be limited to less than 0.5 cm; this smaller margin reduces the radiation delivered to the rectum, bladder, and penile structures.[26] These radiation techniques allow greater radiation dosages to be delivered to the prostate without an associated higher exposure to the surrounding tissues.[6,27,28] Treatment typically involves up to 8 weeks of daily exposures, generally totaling at least 48–45 fractions of 1.7–2 Gy. The recommended dose according to the American College of Radiology is 75–78 Gy but no higher than 81 Gy due to the greater risks of radiation proctitis and cystitis.[6] Currently, the standard of care for EBRT also includes pretreatment with hormonal therapy such as LHRH agonists in order to increase in tumor radiosensitivity.[1,6,29,30]

Focal Therapy

Focal therapy (FT) is another potential treatment option. FT includes high-intensity focal ultrasound (HIFU), focal laser ablation (FLA), irreversible electroporation (IRE), cryotherapy, and photodynamic therapy (PDT), radiofrequency ablation (RFA), and focal brachytherapy.[31] The rise of focal therapy has mirrored advances in MRI technology which has allowed for improved characterization of localized prostatic lesions.[32] Multiparametric MRI (mpMRI) imaging is utilized initially to identify or abnormal areas in the prostate that have high suspicion of cancer. Treatment of these index lesions are the basis of focal therapy as they are believed to drive tumor growth and regulate metastatic risk.[31]

Historically, definitive treatment options of PCa have been limited to radical prostatectomy and radiation which harbor side effects such as erectile dysfunction, urinary incontinence, and radiation cystitis/proctitis. With the development of FT, which spares surrounding structures, patients are at reduced risk of these adverse effects of damaging functional tissue.[31] Structures that are largely spared during most focal therapy operations include the neurovascular bundle, bladder neck, external sphincter and/or rectum.[31] Because of its low complication profile, FT appeals to many patients concerned with the significant morbidity associated with radical treatments.[10,32]

However, FT's effectiveness primarily depends on appropriate patient selection.[31] Ideally, the clinically significant PCa must be able to be predicted and accurately mapped by use of MRI and/or prostate biopsy, localized to the prostate,

access of the prostate through the perineum much be accessible, and treatment efficacy must be able to be assessed.[31] While no overall consensus has been reached to define the ideal FT candidate, many recommendations include PSA < 10 ng/mL, tumor foci of <1.5 mL on mpMRI or <20% of the prostate or <3 mL or <25% of the prostate if contained within a single hemi-gland, and low-/intermediate-risk cancers including Gleason 4+3.[31,33] In short, optimal candidates for FT therapy possess clinically significant intermediate-risk disease that is localized to a single region of the prostate.[33,34] Transperineal template mapping biopsy (TTMBs) is currently the most accurate tool for precise identification of PCa localization and is widely considered the gold standard for identifying FT candidates.[33] Transperineal biopsies are preferred to transrectal as it assesses the prostate in the same plane that treatment will be delivered. It must be noted, that at some intuitions, it requires the use of anesthesia thus incurring an additional cost to its transrectal alternative. While, some urology practices are performing transperineal biopsies in their office under local anesthesia.[35] FT has been found effective in the intermediate term with long-term data currently under investigation.[33,36]

Furthermore, disease monitoring after FT involves the use PSA monitoring. Patients are also offered a prostate biopsy at 1-year post FT to monitor the efficacy of treatment. Prostate biopsies additionally be utilized "for cause": persistence/rise in PSA, abnormal DRE, or concerning MRI findings.[33]

Active Surveillance

Active surveillance (AS) is a widely used standard of care management option for men with low-risk prostate cancer. The goal of this approach is to monitor for any changes in cancer characteristics that increase risk of disease-related morbidity and mortality and identify those who would benefit from definitive treatment.[37] AS therefore allows men with likely indolent disease to defer unnecessary invasive treatment and their associated side effects, thereby maintaining their quality of life.[37–41]

Once patients are started on AS, monitoring protocols are designed to detect progression to higher risk cancer or any misclassifications as low-risk disease.[37] Patients may proceed with definitive radical treatments including surgery and radiotherapy if reclassification in the form of Gleason upgrading occurs.[37] Digital rectal exam and PSA testing are included in the periodic clinical assessment under almost all protocols.[37] A repeat confirmatory biopsy is typically recommended within 1 year of initial diagnosis as well as routine follow-up biopsies every 2–4 years; the presence of clinical indicators of cancer progression may warrant additional biopsy.[37,47,49] Although AS has been shown to improve life expectancy in comparison to watchful waiting, there was minimal improvement in quality of life since many patients on AS eventually received active treatment.[37,53,54] However, the clinical findings used to initiate transition to active treatment often vary patient-to-patient due to the negative impact on patient quality of life associated with definitive treatment.[37] PSA, tumor volume, stage changes, and biopsy changes are all factors that help guide conversations regarding risks and benefits of intervention.[37] Many institutions use both volume of disease and pathologic Gleason upgrading. However, some providers also include PSA >10 while others only deem pathologic upgrading as a sole metric for AS failure. Currently, no consensus has been reached on which factors and thresholds warrant transition to radical treatment; selection criteria is specific to the individual and dependent on patient values.[37]

Patient Reported Outcomes Guide Treatment Selection

In order to properly inform treatment decisions regarding management of localized prostate cancer, a thorough understanding of the long-term patient reported outcomes is critical. Common side effects and complications of the various management options include incontinence, erectile dysfunction, and recurrence of disease. Given the long life expectancy following the majority of prostate cancer diagnoses, knowledge of adverse outcomes may have a significant role in deciding treatments that best preserve patient quality of life.[55] Individual patient values regarding risks of cancer progression and mortality as well as treatment-related sexual, bowel, and urinary dysfunction must be incorporated. Each treatment strategy possesses its own distinct adverse effect profile and comprehensive understanding of the patient-reported outcomes can aid in guiding treatment selection based on individual patient values.

Urinary Incontinence

Urinary incontinence is a condition in which patients suffer from involuntary leakage of urine. Management of urinary incontinence first starts in the pre-operative setting. Pelvic floor exercises are a crucial first step in getting a patient prepared for surgery. After the operation, there are several strategies to manage urinary incontinence. These can include limiting strenuous physical activity for the first 6 weeks, reducing fluid intake, and wearing diapers or pads.[56] In the immediate post-operative setting, many patients suffer from urinary incontinence of varying severity. On average symptoms improve to their new baseline 3–18 months after surgery with 10–15% of men with lingering symptoms. Furthermore after 3 years, this number decreased to less than 10% of all patients.

However, the risk of long-term incontinence is an important outcome metric for patients and their providers. These symptoms can be embarrassing and bothersome to patients and if severe enough, can significantly impair various aspects of their quality of life. As well there is a cost associated with this side effect. Patients require sanitary underwear of liners and other medical supplies to manage their symptoms. Due to socioeconomic constraints, not all patients have access to these medical supplies and/or are able to burden this financial constraint. Urinary incontinence can also lead to development of urinary irritative symptoms such as incontinence-associated dermatitis due to prolonged contact with urinary irritants and exacerbation of frictional forces from increased skin moisture; along with pain or discomfort, skin barrier damage can also occur, predisposing to secondary infections.[57] In addition, many patients may find the condition of urinary incontinence itself shameful, which can result in a negative impact on their self-esteem and body image.[56,58]

The presentation of urinary incontinence symptoms following prostate cancer treatment varies according to the treatment and patient characteristics. When comparing definitive treatment options, surgical therapy with radical prostatectomy is more likely associated with the risk of urinary incontinence when compared to radiotherapy.[59] The Prostate Testing for Cancer and Treatment (ProtecT) trial from the United Kingdom reported the 150-year outcomes of patients managed with AS, prostatectomy, and radiotherapy for localized PCa. In this study, the survival rate for all three treatment groups were similarly high; however, prostatectomy was associated with the poorest urinary continence outcomes, in comparison to groups managed with AS and radiotherapy.[26,60] Although radiotherapy was found to have worse urinary and bowel symptoms at 6 months, there was a considerable amount of recovery; these effects were comparable to the other groups after 12 months.[26,60] These results indicate that for low and intermediate risk PCa patients, prostatectomy, radiotherapy, and AS may likely yield similar PCa-specific mortality, but radiotherapy may better avoid long-term incontinence in comparison to prostatectomy.[26]

Furthermore, outcomes associated with urinary incontinence have been investigated by several institutions. Barocas et al in 2017 assessed patient reported quality of life changes. This group found that radical prostatectomy was associated with significant urinary incontinence decline 3 years after treatment, while patients who had received radiotherapy or were on active surveillance had no significant change in urinary incontinence compared to baseline.[61] A similar study in 2023 found that 12 years after treatment, almost a quarter of the patients who had undergone prostatectomy had urinary leakage, defined as wearing one pad or more per day, compared to 8% of the patients who had received radiotherapy.[55] 3% of the patients on AS reported urinary leakage which was speculated to represent age-related changes to urinary function.[55] These statistics were comparable when the three treatment type groups were analyzed based on age relative to 65 years of age.[55] However, radiotherapy and active surveillance are associated with greater urinary irritative symptoms, such as nocturia and urgency.[55,61] By 12 years post treatment, 48% of patients who had undergone radiotherapy and 34% of patients who had undergone prostatectomy reported nocturia, defined as voiding at least twice per night.[55] The authors further concluded that a prostatectomy had a lower rate of irritative symptoms because the operation inherently treats any preexisting bladder outflow obstruction, contributing to improved urinary flow.[55] Overall, the 2023 study found that 11% of the patients who had undergone prostatectomy and 7% of patients who had undergone radiotherapy felt as though their urinary symptoms had a significant impact on their quality of life 12 years after therapy.[55]

Urinary incontinence can further be subdivided based on prevailing symptoms. Stress incontinence is the most common subtype of incontinence associated with RP.[59] Coelho et al evaluated the 1-year outcomes of localized prostate cancer patients treated with retropubic radical prostatectomy (RRP), laparoscopic RP (LRP), and robot-assisted radical prostatectomy (RARP); they found that 79%, 84.8%, and 92% of patients were continent 1 year after treatment with

higher continence rates reported at high volume RP centers with high volumes of prostate cancer surgeries.[59,62] This suggests that physician expertise and surgical center may also help predict outcomes and guide treatment decisions for patients considering prostatectomy. Many men typically experience some improvement in urinary continence over time following prostatectomy; however, late onset recurrence of incontinence has been reported.[59] Naselli et al found that approximately 10% of patients who had initially achieved total continence following prostatectomy eventually became incontinence again at a median follow-up of 100 months.[59,63] This has been hypothesized to be linked to age-associated loss of sphincter tone/mass which was escalated by RP-related changes in anatomy.

Post-prostatectomy incontinence outcomes may also be influenced by patient characteristics. Older age at the time of surgery has been found to be associated with worse postoperative incontinence outcomes.[59,64,65] Individual patient anatomy may be another predictor of incontinence outcomes following prostatectomy. Longer urethral length on MRI was found to be associated with superior continence outcomes overall as well as a shorter time to achieve continence following surgery, possibly due to lower risk of sphincter complex damage.[59,65] Poorer overall continence outcomes were also associated with larger MRI prostate volumes.[59,65] Obesity is another potential predictor of continence outcomes as well. A study by Roermund et al reported that there was a significantly greater likelihood of persistent incontinence (25.8%) in obese men who underwent radical prostatectomy compared to non-obese men (8.7%) ($p < 0.05$).[65,66] A study by Wolin et al later confirmed their findings by showing 26% lower risk of persistent incontinence in non-obese, physically active men compared to their obese counterparts (RR 0.74, 95% CI 0.52–1.06).[67]

While RP has a significant risk of urinary incontinence, RT is not without risk as well. Urinary urgency, frequency, and urge incontinence can develop in some radiation-treated prostate cancer patients who received either EBRT or BT with radioactive seed implants; stress incontinence, however, is relatively rare.[24,59,68,69] These can often include urinary frequency and urgency, urinary incontinence, dysuria, and hematuria, the severity of which can vary according to the dosage of radiation, proximity to the irradiated region, and the unique anatomy that exists with each patient. These side effects may arise during therapy and persist following cessation for up to several months.[24] Various lifestyle changes may be required to alleviate these symptoms, such as reducing fluid intake, eliminating consumption of caffeine and alcohol, and strengthening pelvic floor muscles, which may be augmented by pharmacological interventions.[24,70]

BT was also found to be associated with increased risk of urinary retention in the immediate postoperative period. Many of the acute tissue changes and edema that cause initial bladder irritation resolve over time. A study Anderson et al found that urinary symptoms typically had complete resolution within 1 year and continued to be reasonably well-maintained at 5 years.[59,71] However, pelvic radiation-produced alterations in urinary patterns may not be immediate and often emerge long after treatment has been completed. In a long-term follow-up study of men who had received EBRT, the prevalence of urinary incontinence symptoms showed a significant increase between 8 and 15 years following treatment, the risk of which may have been higher in patients who had prior surgical therapy.[72] A study by Odrazka et al similarly found that prior prostate surgery was associated poorer continence outcomes following treatment with conformal or intensity modulated radiotherapy; 23% of men who had undergone prior prostate surgery experienced severe urinary incontinence compared to 9% of men who had not.[59,73]

Improvements in radiation techniques over the past decade have led to enhanced preservation of adjacent benign structures thereby reducing the bowel, urinary, and sexual side effects.[26] Advances in radiotherapy delivery methods include conformal techniques, proton and photobeam, and other approaches which may improve continence outcomes. Talcott et al report that conventional radiation and high-dose combined proton and photon radiation did not affect voiding outcomes; there was also no statistical difference in urinary irritation, obstruction, and incontinence symptoms at a median follow-up of 9.4 years.[74]

Radiation Cystitis

Pelvic radiation on the genitourinary system may cause inflammation of the bladder lining, ultimately resulting in radiation cystitis; symptoms may range from mild voiding discomfort to serious hemorrhagic cystitis.[75] Lower urinary tract symptoms can include dysuria, urinary frequency, urinary urgency, and incontinence.[76] Radiation-induced hemorrhagic cystitis (RHC) is the most life-threatening complication and a fearsome late complication of prostate RT and severe form of radiation cystitis, can present anywhere from 6 months to 20 years post-radiotherapy. Hematuria is most

common presenting symptom of radiotherapy-related urologic hospital admissions.[75,77] Hematuria can also lead to secondary clot formation and urinary retention.[76] Sanguedolce et al found that 5.6% of patients in a cohort of 1421 patients post-RT for PCa developed RHC. 55% of the patients that developed RHC were admitted for a urologic emergency, and the remaining 45% were hospitalized.[77] All 80 patients with RHC underwent bladder washout, 22 required TUF, and 8 received consolidation therapy with either hyaluronic acid (HA) or hyperbaric oxygen therapy (HBOT). In 2012, it was shown that HA and HBOT are equally effective consolidation therapies[77] in preventing the recurrence of hematuria.[77,78] Of the 36 patients that were hospitalized, 14 (38.9%) required blood transfusions and 6 (16.6%) required cystectomies.[77] Of the 6 that had undergone radical cystectomies, 2 were diagnosed with metachronous bladder urothelial cancer, 3 had failed treatment of non-remittent hematuria with consolidation therapy, and 1 had severe dysuria secondary to a poorly compliant bladder, a common presentation of radiation cystitis.[77] Almost half of the patients that received consolidation therapy failed treatment and required a cystectomy, emphasizing radiation-induced hemorrhagic cystitis' profound level severity.[77]

Based on the severity, duration, and timing of the patient's symptoms, treatment options can include systemic medications, intravesical therapies, and more invasive surgical interventions.[75] Continuous bladder irrigation (CBI) is the first line treatment for RHC and facilitates evacuation of blood clots (Goucher, 2019).[79] Tranexamic acid (TXA) has been used with CBI as a conservative treatment, but studies have yet to present robust data.[75,80] Cystoscopy should be performed on all patients to exclude bladder malignancy and confirm the diagnosis of radiation cystitis characterized by pale mucosa, diffused telangiectasia, or ulcerations.[77,80] Transurethral fulguration (TUF) can be performed during cystoscopy on suspected lesions to provide possible hematuria relief.[77,79,80] As an alternative to TUF, laser ablation has been well tolerated by patients and has shown complete response in 75–97.5% of cases.[79,80]

Further treatment options include systemic therapies such as sodium pentosan polysulfate (SPP), which has shown complete resolution of RHC symptoms in some chronic cases, but is not indicated for acute hematuria.[75,80] Intravesical therapies can include substances such as aluminum, formalin, silver nitrates, epsilon aminocaproic acid (EACA), or HA and have shown varying degrees of efficacy. A study of 40 patients with RHC treated with intravesical aluminum reported symptom resolution in approximately 60% of cases.[81] Formalin has shown a 71–89% clinical response rate, typically achieving complete response within 48 hours of a single instillation.[75,79] Despite better outcomes, formalin is associated with a worse side effect profile and requires anesthesia.[79,80] Silver nitrate has been largely ineffective at treating RHC, EACA has not been studied since 1992 but demonstrated resolution of hematuria in 37 out of 39 patients with radiation or chemotherapy-induced cystitis. HA has shown partial or complete response rates in some studies up to 92% comparable to HBOT.[77,79,80] HBOT induces neo-angiogenesis, restoring up to 80% of capillary density lost due to tissue ischemia and necrosis in RHC.[80] Complete hematuria resolution with HBOT has been reported in 34–87.5% of patients, but if initiated within six months of symptom onset potential resolution is increased up to 96%.[80]

In cases where conservative and nonoperative measures fail, surgical intervention or embolization may be necessary.[75,80] A surgical option may include urinary diversion, a procedure that redirects urine flow out of the body via cutaneous ureterostomy, ileal conduit, or bilateral nephrostomy tubes.[79,80] However, this procedure has been associated with a 40–50% mortality rate in some case.[79,80] Embolization has also been studied in small case series with mixed results. Different cohorts have found complete resolution of intractable hematuria in 81–100% of patients, but they have also found mortality rates as high as 20–66% and ischemic complications in 10–62.5% of patients.[75,79,80] While surgery and embolization remain options for chronic and refractory cases of RHC, further research is needed before they become more widely adopted.

Bowel Incontinence

In addition to bladder side effects, bowel side effects are often common and particularly associated with radiation.[6,82] Radiation proctitis refers the collection of GI symptoms caused by the radiation-induced inflammation of the rectal mucosa.[24] Different patients may experience varying severity of GI symptoms, which can include diarrhea, rectal pain, fecal urgency and frequency, fecal incontinence, straining, and rectal bleeding.[24,83–86] It has been suggested that radiotherapy causes a greater decline in bowel function and increased bowel-related irritative symptoms compared to other treatment options, but the impact this has on patients' quality of life may not be as significant as we had

expected.[55,61] Barocas et al found that bowel urgency at 3 years was lower for patients who received RP than those who received EBRT (3% vs 7%, OR 0.3 [0.2, 0.6].[61] In the ProtecT trial, Donovan et al reported that fecal leakage gradually increased in the radiotherapy group and came to affect twice as many patients (12%) as post-prostatectomy and post-active monitoring patients (6% each) after 12 years post-treatment.[55] The radiotherapy group also initially experienced worse hematochezia but this resolved by 7–12 years; the incidence of loose stools, and impact of bowel symptoms on quality of life were also comparable after 12 years following radiotherapy, prostatectomy, and active monitoring.[55]

Erectile Dysfunction

Erectile dysfunction (ED) is another major complication that frequently follows treatment of prostate cancer by radical prostatectomy, EBRT, brachytherapy, a to a lesser extent of FT cases.[87–89] This condition is defined as the inability to achieve or maintain a sufficient erection for satisfactory sexual intercourse. Any component of the erectile response can be altered in ED, including organic, relational, and psychological.[90] Sexual dysfunction can negatively impact men's quality of life and lead to symptoms of depression and sexual performance anxiety, which can affect the sexual experience of the partner and couple's quality of life.[90]

Similar to the outcomes for urinary and bowel incontinence, the ProtecT trial found that compared to AS and radiotherapy, prostatectomy was associated with poorer long-term sexual function outcomes following treatment.[55] Between years 7 and 12 post-treatment, around 42% of patients that had undergone a prostatectomy reported that their declined sexual function had a moderate-to-severe impact on their quality of life.[55] In comparison, this same impact was reported in 37% of patients undergoing active monitoring and 30% of patients who had undergone radiotherapy).[55] Another study by Wortel et al found that 30–45% of men who were initially potent reported erectile dysfunction following EBRT.[6,91]

Radical prostatectomy has a high risk of operative injury to the cavernous nerves due to their close proximity to the prostatic capsule and seminal vesicles, which are removed with the prostate gland. Additionally, ED is also closely related to the resulting corporal smooth muscle damage, with a majority of men experiencing venous leakage rather than arterial insufficiency which is thought to be secondary to hypoxia-induced fibrotic changes of the penis.[59,87,88] There is wide variation in the rates of ED following radical prostatectomy in the literature, which can range from 10–100%.[59,92] Several factors impact outcomes including surgical technique, surgeon volume and experience, patient age, preoperative erectile function, post-surgical erectile hemodynamic changes, and quality of surgical neurovascular bundle preservation.[59,93]

Radiotherapy can also damage the surrounding nerves and vasculature critical for achieving and maintaining erections; this can result in sexual dysfunction that ranges in severity from moderate difficulty to complete impotence.[24,94,95] 20–80% of patients experience ED following radiotherapy.[59,96] The effects of radiotherapy on sexual function can be acute (reduced libido, difficulty achieving and maintaining erection, and reduction in erection quality) or long-term (persistent erectile dysfunction, overall decreased sexual gratification).[24,97] ED following EBRT and/or brachytherapy is believed to be the result of radiation-induced microvascular endarteritis of the penile vasculature, proximal corporal fibrosis, and/or acceleration of pre-existing atherosclerosis; ED symptoms commonly present insidiously and progressively.[87] Radiation dose modality is the primary predictor of ED after radiotherapy.[59] A study by Namiki et al comparing erectile function outcomes following radiotherapy reported that intensity modulated radiotherapy produced better results compared to 3D conformal radiotherapy and conventional radiotherapy in preserving erectile function.[98] Al-Abany et al still found 3D conformal radiotherapy to be superior to conventional radiotherapy in the preservation of erectile function.[99] Although the neurovascular bundle's proximity to the peripheral zone makes dose limitation to this area difficult, radiotherapy spares the penile bulb, rectum, and nerve blood supply; therefore, compared to prostatectomy, the chance of preserving erectile function is higher.[59] In BT-related ED, radiation dose to the proximal penis has been implicated.[100] A prospective study by Merrick et al found that 50% of patients experienced BT-induced ED at 3 years.[101] Multivariate analysis showed that the strongest predictors of BT-related ED were pretreatment erectile dysfunction and proximal crura radiation. Consequently, preservation of erectile function may be improved by approaches that minimize radiation to the proximal penis.

Androgen receptor antagonists and LH-releasing agonists and antagonists used in combination with RT has also been linked to sexual dysfunction. These drugs are often associated with decreased libido, erectile dysfunction, delayed or absent ejaculation, and anorgasmia.[102] In addition, responses to treatments such as PDE5 inhibitors and self-administered intracavernous injections have been found to be reduced when taking this medication.[87]

The possibility of secondary erectile dysfunction and its management options should be discussed with the patient prior to starting any definitive therapy. Oral phosphodiesterase type 5 inhibitors, vacuum devices, intracavernosal injections, and penile prosthetic implants are all options for managing post-treatment sexual dysfunction.

Fatigue

Mild to severe fatigue is also a commonly reported symptom associated with radiotherapy for PCa. Radiation therapy can trigger the release of pro-inflammatory cytokines, which can activate the inflammatory response and trigger the immune system to release chemicals that promote fatigue.[24,103,104] Radiation therapy can also disrupt the body's circadian rhythm, causing fatigue and other sleep disturbances.[24,105] Radiotherapy-induced fatigue is managed with rest, good sleep hygiene, energy conservation, a nutrient-rich diet, and stimulants.[106–108]

Oncologic Control

The goal of radical prostatectomy is to improve overall survival and reduce risk of subsequent metastasis for cases of localized prostate cancer.[6] However, these benefits only become evident beginning around 10–12 years after treatment and have the greatest impact in men diagnosed at ages younger than 65.[6] The outcomes of several case series have suggested a good disease-free survival rate for patients with early prostate cancer treated with radical prostatectomy. A study by Han et al found that the 5-, 10-, and 15-year probabilities of localized control (ie PSA > 0.2 ng/mL) for clinically localized prostate cancer treated by radical prostatectomy was 84, 72, and 63%, respectively. The authors also reported the corresponding probabilities of metastases-free survival were 96, 89, and 81%, respectively.[109] A different study by Pound et al reported the median time to biochemical failure to be 8 years and the median time to metastases following biochemical failure to be 5 years.[110]

Radiotherapy has been found to yield comparable oncologic control to prostatectomy. A study by Kupelian et al found similar biochemical failure rates following higher-dose radiation (≥72 Gy) and radical prostatectomy.[111] Disease-free survival was also found to be similar between radiation and radical prostatectomy in several case series.[112,113] EBRT and BT were found to have similar efficacy.[114,115] There may be increased risk of secondary cancers in areas treated with radiotherapy or other regions of the body; however, this is rare.[24,116,117] Compared to whole gland treatment in the form of RT or RP, FT has a more favorable side effect profile and with similar comparable oncological control in a short to midterm intermediate period follow-up in the current literature.[31] It may therefore be preferable in cases in which the benefits reduced sides and post-operative complications outweigh of oncological control.[6] However, FT's effectiveness in controlling and/or curing localized prostate has not been established in long-term dataset and is currently considered for men whose data is prospective collected.[6] Reddy et al report that focal HIFU provides reliable intermediate-term oncologic control over 7 years but 10-year data has not yet become available.[118] In previous patients treated with FT for localized prostate cancer, there have been several cases in which disease has recurred.[31,36,119] Further advances in imaging and navigational technologies and PCa mapping may be necessary to better stratify FT-eligible patients and improve recurrence rates.[31]

Additionally, most of the studies on FT outcomes for treatment of localized PCa are still in early research stages and long-term oncologic control of this treatment has yet to be definitively proven.[31,34] Many other questions must also be addressed before FT can be considered a n alternative standard PCa treatment option; these include each ablative therapy's functional and oncological outcomes, the normal tissue margin required, and long-term disease recurrence.[33] Many patients may require either 2nd-line treatment or active surveillance.[120] In patients for whom FT fails, viable alternatives include prostatectomy and radiation therapy.

At the same time, the value of treatments with oncologic control may vary patient-to-patient. Bhatnagar et al estimated quality-adjusted life years (QALYs) using decision modeling for clinically localized prostate cancer patients. They found that there was a decreased number of QALYs in patients with Gleason 2–4 cancer following treatment, and

an increased number of QALYs in patients with Gleason 7–10 cancer following treatment. This might indicate that clinically localized Gleason 2–4 cancer is not associated with shortened life expectancy and conservative management may be reasonable to avoid long-term side effects. In contrast, for patients with Gleason 7–10 cancer, definitive treatment such as surgery or radiation should be considered due to high risk of cancer-related mortality and improved disease-free survival following treatment. Patients with moderately differentiated cancer or Gleason 5–6 cancer should evaluate their personal risk factors such as age and overall life expectancy.[121] In many cases of prostate cancer, whole-gland treatment's benefits of oncological control are outweighed by its risk complications, and side effects. In select patients with a single, isolated lesion of Gleason 7 without evidence of extraprostatic disease, focal therapy may be preferable due to its significantly fewer side effects as well as its lower costs in comparison to traditional whole-gland treatment.[6]

Patient Counseling and Expectation Management

The variety of prostate cancer management options, lack of established superiority of a single treatment modality, and the presence of physician bias all complicate treatment decision making.[122] Therefore, clinicians should comprehensively educate their patients on the various treatments and their overall outcomes in order to tailor treatment to the patient's individual goals, whether that be oncologic control or preservation of sexual function or maintenance of normal day-to-day operations. The overall goal is building a treatment plan that maximizes a patient's satisfaction and aligns with his clinical priorities. Figure 1 is comprehensive pictorial review of treatment complications between radiotherapy and prostatectomy based on a recent publication of 12-year data.[123]

Sandra et al conducted a prospective study on quality of life measures reported by 1201 patients and 625 spouses after radical prostatectomy, EBRT, and BT. They found that all 3 groups experienced impaired sexual dysfunction. Urinary incontinence was found after radical prostatectomy. Urinary irritation and obstruction occurred after radical prostatectomy, EBRT, and BT but improved over time. Overall, they concluded that each definitive prostate cancer treated had its own unique toxicity profile.[20,122,122]

Compared to definitive treatment, AS has been found to have reduced adverse effects. Hayes et al reported that greater quality-adjusted life expectancy was associated with AS in comparison to definitive treatment management.[124] Greater urinary continence and erectile function were also associated with expectant management compared to immediate treatment.[125]

The side effects of each treatment options are important to cover, however the first step in an informed shared decision-making discussion is to evaluate and ensure patient trust. It is important that patients feel that they can trust their physician to have their best health outcomes in mind and properly inform them.[126] Strong physician-patient trust is linked to high information disclosure, patient satisfaction and adherence, and improved health outcomes.[126,127] A good relationship with their physician may allow patients to feel more comfortable providing full disclosure of their personal goals and concerns. Physician empathy is a strong component of establishing a positive physician-patient relationship. Displays of empathetic behavior such as showing attentiveness toward their patient's feelings, expressing understanding of their perspective, assuaging their worries, and supporting with their individual needs, physicians may build better trust with their patients.[126,128,129] It has been shown that patients' overall trust as well their trust in their physician's benevolence and competence can be directly influenced by their perception of physician empathy.[126] Therefore, the first step in creating a well-formed treatment plan is building a strong patient-physician physician relationship in which the patient trusts his physician to understand and address his major concerns and needs. This might require repeat office visits to review treatment plans and adjust to each unique individual. Once this relationship is established, physicians should work alongside their patients to determine which treatment will best meet their goals and minimize regret. Providing a comprehensive education regarding patients' cancer and overall health status allows them to better understand their current condition and what their treatment options are.

Following this, physicians must also appropriately educate their patients on the various treatment options available. This should also include a comprehensive discussion regarding patients' individual and cancer-related characteristics, likely treatment outcomes, and potential complications. Patients should leave with a thorough understanding of the risks and benefits of each treatment based on their health status and goals. This becomes especially important in treatment of

Event	Prostatectomy	Radiotherapy
Urethral struicture	+	++
Placement of artifical urehtary Sphincter	+++	+
Placement of Penile Prosthesis	++	++
Erectile Dysfunction	++	+
Urinary Incontinence	++	+
Radication Cystitis	---	+++
Radication Proctitis	---	+++
Secondary Bladder Cancer	---	+
Need for Cystectomy	---	+
Secondary Rectal Cancer	---	---
Any Complication	++	+
Oncologic Control	+++	+++
"---" = Compareable to unaffected population	*Odds ratio calculated within a combined cohort of patients who underwent Prostatectomy or Radiotherapy with 12 years of follow-up	
"+" = Odds ratio between 1 - 5		
"++" Odds Ratio between 5 - 20		
"+++" Odds Ratio >50		

Figure 1 Risk of sequela by type of prostate cancer treatment.

diseases with relatively long-life expectancy such as prostate cancer. By properly educating patients so they can make informed decisions about their health, physicians can maximize patient autonomy and minimize regret.

While treatment plans can be tailored according to the individual needs of a patient, no treatment is without risk of adverse side effects or failure. Clinicians should manage patient expectations by providing comprehensive information regarding the overall likelihood of complications and side effects of each treatment. Understanding the risk profiles of each treatment is especially important because different patient-reported outcomes such as urinary incontinence may be more or less bothersome depending on individual patient factors including age, occupation, and social activity.[55] Presenting patients with comprehensive data allows them to reach their own personal conclusions about the relevance of each the reported outcomes and reduce decisional regret due to insufficient understanding of treatment adverse effects.[55] Overall, the ProtecT trial found that treatment-related effects on urinary, bowel, and sexual function may persist and even worsen over time for patients treated with prostatectomy or radiotherapy. In particular, prostatectomy was associated with severely impaired sexual dysfunction and persistent urinary leakage in 20–24% of participants after 12 years. Throughout the trial, the prostatectomy-treated patients experienced the greatest impact on sexual function with minimal recovery and further decline over time. For the radiotherapy-treated patients, there was some recovery after the immediate reduction in sexual function, but over time, there was a gradual decline. 7% of the radiotherapy treatment group also reported symptoms of urinary leakage that had a moderate-to-large interference with life.[55] A later study by Chen et al assessed quality of life outcomes associated with more contemporary treatments and found results similar to the ProtecT trial across treatment groups after 2 years: sexual dysfunction and urinary incontinence were associated with radical prostatectomy, whereas short-term urinary obstructive and irritative symptoms and bowel problems were associated with radiotherapy.[130]

Appropriate preoperative counseling must include a thorough assessment of a patient's individual risk factors and their potential impact on treatment outcomes. Cancer grade can be a predictor of life expectancy and appropriateness to actively treat. In addition to characteristics of the cancer itself, overall patient characteristics may play a role. The risk of developing erectile dysfunction and urinary side effects following whole-gland treatment increases with patient age and comorbidities.[131,132] Additional outcome predictors such as hospital volume and procedure approach should be included in discussion as well. Hospitals that perform higher numbers of prostatectomies are associated with lower complication rates. Unilateral or bilateral nerve sparing surgery yields lower incidence of postsurgical erectile dysfunction. Bladder neck- and distal urethral sphincter-sparing approaches are associated wither fewer urinary side effects.[59]

Counseling should also include discussion of disease recurrence and potential need to escalate treatment in the future. For patients diagnosed with localized, potentially curable prostate cancer who otherwise have a reasonable functional status, a satisfactory quality of life, and a life expectancy greater 10 years, both surgical and radiation therapy should be included in patient-provider discussions regarding treatment selection.[6] There are significant side effects typically associated with definitive therapy; therefore, these discussions should include suitable options that balance therapeutic goals such as longer survival, cancer cure, and potential recurrence with impact on quality of life due to treatment side effects, complication risks, and financial burden.[6] For these reasons, clinicians have been increasingly utilizing active surveillance for men with intermediate favorable prostate cancer. Active surveillance allows when to delay definitive management, on average of 2–4 years, without a meaningful change in oncologic control. AS for this patient cohort, allows men to live without the side effects of definitive therapy for a time.

Alternatively, FT has also seen increased utilization for intermediate risk disease. Before initiation of FT, clinicians should properly counsel patients on the possibility of disease recurrence and provide information about available management options if FT fails. No consensus currently exists regarding optimal management for disease recurrence in patients who received FT and there are few studies on the toxicity profiles of these additional treatments following FT.[119] Radical prostatectomy is one option. In a multicenter cohort study of 82 patients who received salvage robotic-assisted radical prostatectomy (S-RALP) after FT, S-RALP following FT was found to be associated with worse erectile function outcomes compared to primary RALP but had comparable postoperative continence rates, perioperative outcomes, positive margin rates, and complications.[119] S-RALP following FT was also found to have a relatively high biochemical relapse rate (PSA $\geq$ 0.2 ng/mL), specifically in men who experienced an infield recurrence, compared to primary RALP patients.[119] This may be due to development of "ablation-resistant" clones following initial incomplete ablation, which repopulate the ablation field and spread locoregionally. However, this is highly speculative at this point in time.[119]

Conclusion

Given the relatively long-life expectancy and multitude of currently available treatment options for prostate cancer, patient preferences have come to play a central role in disease management. Thorough discussion of patient-reported outcomes can guide decision-making by optimizing treatments that maximize quality of life and minimize the specific complications each individual patient considers most undesirable. The most commonly reported treatment-related complications include erectile dysfunction, bowel and urinary incontinence, and cancer recurrence. Proper management entails an open, comprehensive discussion between the patient and his physician that includes the patient's individual goals and the efficacy and risks associated with each treatment option. Appropriate education, expectation management and counseling can establish patient autonomy in managing their own health decisions and minimize regret.

Disclosure

Dr Louis Krane reports personal fees from AngioDynamics, MDx Health, Sonablate, and HIFU Prostate Services, during the conduct of the study. The authors report no other conflicts of interest in this work.

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