

# The Impact of Prostate Cancer Treatment on Quality of Life: A Narrative Review with a Focus on Randomized Data

This article was published in the following Dove Press journal:  
*Research and Reports in Urology*

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**Abstract:** Despite excellent oncologic outcomes, the management of localized prostate cancer remains complex and is dependent on multiple factors, including patient life expectancy, medical comorbidities, tumor characteristics, and genetic risk factors. Decades of iterative clinical trials have improved the optimization and utilization of surgical and radiation-based modalities, as well as their combinatorial use with anti-androgen and systemic therapies. While cure rates are high and converging on equivalent disease control should an upfront surgical or radiotherapeutic approach be optimized, the long-term side effects of surgical and radiation-based treatments can differ significantly in nature. Decisions regarding the selection of therapy are therefore best made in an informed and shared medical decision-making process between clinician and patient with respect to cancer control as well as adverse effects. We outline in this narrative review an understanding regarding implications of surgical and radiation treatment on quality of life after treatment, and how these data may be considered in the context of advising patients regarding the selection of therapy. This narrative review largely focuses on the quality of life data obtained from prospective randomized trials of men treated for prostate cancer. We believe this provides the best assessment of the quality of life and can be used to inform patients when making treatment decisions.

**Keywords:** prostate cancer, radical prostatectomy, radiation therapy, quality of life, toxicity

## Approaches for Clinically Localized Prostate Cancer

Estimated 191,930 new cases of prostate cancer will be diagnosed in the United States in 2020, accounting for 21% of new cancer cases in men.<sup>1</sup> Overall prognosis, especially in the setting of localized disease, is extremely good with five-year relative survival greater than 98% for all races between 2009 and 2015. In general, men who are older and have very low-risk prostate cancer may not benefit from active intervention and instead may choose a strategy of watchful waiting<sup>2</sup> (Table 1). For men who have longer life expectancy and low-risk disease, active surveillance, radical prostatectomy (RP), external beam radiation (XRT), and brachytherapy (BT) are all options supported by the National Comprehensive Cancer Network (NCCN) guidelines.<sup>3–7</sup> With regard to the radiation treatment course, conventional fractionation, hypofractionation, and stereotactic body radiotherapy (SBRT) may all be considered options based upon individual risk assessment, as well as tumor and treatment characteristics.<sup>8–12</sup> NCCN favorable intermediate-risk disease (<50% of cores positive, no Gleason Grade Group 3 or higher histology,

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**Table 1** Treatment Selection for Localized Prostate Cancer, Stratified by Risk Group

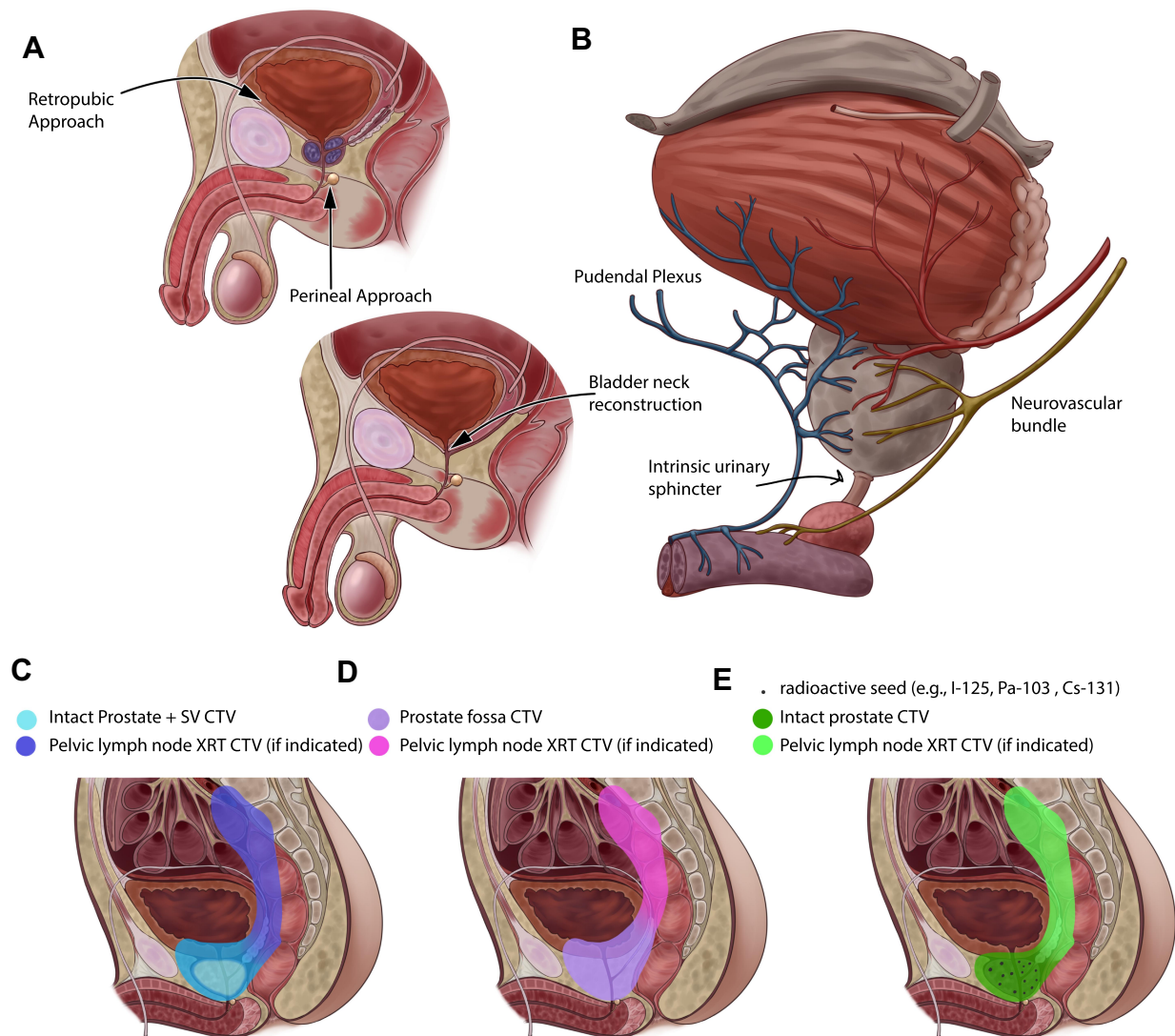
Disease Group	Treatment Modalities
Low-Risk	If expected patient survival $\geq$ 10 years, active surveillance, external beam radiation (standard fractionation, hypofractionation, or SBRT), brachytherapy (HDR or LDR), and radical prostatectomy are all options; if $<$ 10 years, observation is recommended
Favorable Intermediate-Risk	If expected patient survival $\geq$ 10 years, active surveillance, external beam radiation, brachytherapy, and radical prostatectomy are all options; if $<$ 10 years, observation, external beam radiation, or brachytherapy is recommended
Unfavorable Intermediate-Risk	If expected patient survival $\geq$ 10 years, radical prostatectomy, external beam radiation with 4–6 months of ADT, external beam radiation and brachytherapy boost and 4–6 months of ADT are all options; if $<$ 10 years, observation, external beam radiation with 4–6 months ADT, and external beam radiotherapy and brachytherapy boost and 4–6 months ADT are all options
High-Risk	If $>$ 5 years or symptomatic, external beam radiation with 18–36 months ADT, external beam radiation and brachytherapy boost and 18–36 months of ADT, and radical prostatectomy are all options; if $\leq$ 5 years and asymptomatic, observation, external beam radiation and ADT are all options
Adjuvant/Salvage	If adverse features (positive margins, seminal vesicle involvement, and/or extraprostatic extension), consider adjuvant external beam radiation; otherwise, close monitoring with external beam radiation and 6–24 months of ADT recommended if clinical or biochemical evidence of failure

only one intermediate-risk factor) has a treatment algorithm that is similar to low-risk disease.<sup>13</sup> Unfavorable intermediate-risk and high-risk diseases typically require the addition of androgen deprivation therapy (ADT), as well as potentially a brachytherapy boost, to external beam radiotherapy.<sup>6,14–20</sup> Regarding length of ADT, unfavorable intermediate-risk disease and high-risk disease typically require 4–6 months and 18–36 months, respectively, with currently less level 1 data regarding justifying the optimal length of ADT in the setting of brachytherapy boost.<sup>6,21–25</sup> The addition of systemic therapy, e.g. docetaxel, to radiation has been historically more controversial and individualized in the context of high-risk, localized disease, though recent data from the GETUG 12 trial as well as RTOG 0521 have suggested superior 8-year relapse-free survival and 4-year overall survival, respectively.<sup>26,27</sup> Given the limited data, however, the addition of docetaxel to ADT plus XRT in high- or very high-risk prostate cancer is not categorically recommended as of NCCN Version 2.2020 until longer follow-up demonstrates comparable success of salvage treatments and rates of long-term adverse effects.

External beam radiation often incorporates pelvic nodal treatment when there is a threshold risk of lymph node involvement, e.g. 15% or higher<sup>28,29</sup> (Figure 1). This risk is estimated based on clinical factors such as Gleason Score (GS) and Prostate Specific Antigen (PSA), often with the assistance of a nomogram. RTOG 0924 trial is

underway to provide further insight into the definitive RT setting. Postoperatively, XRT and ADT still may be a requirement in the adjuvant setting depending on factors such as lymph node involvement, positive margins, extraprostatic extension, and seminal vesicle involvement.<sup>30–34</sup> If adjuvant treatment is not pursued based on favorable pathology, salvage radiation to the disease bed or pelvis, as well as ADT, still is required if there is clinical or biochemical evidence of failure,<sup>35,36</sup> with the extent of nodal treatment additionally under investigation in the salvage setting.<sup>37</sup>

The first generation of meta-analyses utilizing observational data compared surgical and radiation-based modalities across all risk groups of localized disease with regard to overall mortality (OM) and prostate cancer-specific mortality (PCM) hazard ratios, the most well known of which found OM and PCM benefits to upfront surgery across all groups.<sup>38</sup> Additional efforts found that controlling for quality of ADT, adequate radiation dose, and overall compliance with modern NCCN standard-of-care diminished these differences.<sup>39,40</sup> There is even a suggestion of improved PCM for RT-based modalities compared with RP in the setting of Gleason 9–10 disease when BT is used with XRT, though there are limited observational data available to answer this question.<sup>41–44</sup> There is some evidence that this advantage for brachytherapy boost diminishes in the setting of RP plus adjuvant RT.<sup>43,44</sup> Should these data prove verifiable



**Figure 1** Surgical and Radiotherapeutic Approaches in the Treatment of Prostate Cancer. **(A)** pre- and post-prostatectomy anatomy with retropubic and perineal surgical approaches. **(B)** microsurgical anatomy at risk for injury with retropubic and surgical approaches. **(C)** clinical target volumes (CTV) for radiotherapy for intact prostate treated definitively with external beam radiotherapy (XRT). When indicated pelvic lymph node fields are added, increasing the potential for gastrointestinal toxicity. **(D)** CTV for radiotherapy for prostate fossa treated adjuvantly or in salvage cases. The utility of lymph node coverage in this setting is the subject of clinical investigation. **(E)** CTV for low-dose-rate brachytherapy with or without XRT treatment. High-dose-rate techniques are available using temporary catheter-based placement of an Ir-192 source with established fractionation schedules and fewer post-treatment radiation precautions.

with prospective data, there may be a subset of patients with Gleason 9–10 or other high-risk diseases for which a discussion of treatment options may converge on XRT +BT with ADT versus RP with a very strong possibility of requiring adjuvant RT. Counseling patients regarding the burden of GU-related toxicity associated with BT-boost is substantially different if the pre-procedural probability is high that adverse features will prompt adjuvant radiation to the prostatic fossa and possibility pelvic lymph nodes.

Given the high rates of success for oncologic outcomes as well as more robust algorithms to achieve similar oncologic outcomes with upfront RP or RT, there is a need to better understand the toxicities of various treatment modalities and how they affect patient quality of life. To help providers with this important conversation, we have provided a narrative review of the data involving treatment-related toxicity and potential interventions to ameliorate toxicity during and after treatment.

## Methods

We performed a search of the PubMed database to identify pertinent articles that included quality of life assessments relating to the treatment of prostate cancer and common treatment modalities including RP, XRT, BT, and ADT. The search focused on randomized clinical trials comparing treatment modalities for prostate cancer that included quality of life metrics. In addition to database searches, hand searches were also conducted based on expert opinion and author consensus. Studies including intraoperative fresh-frozen pathologic analysis of margins to improve nerve sparing during RP or injection of hydrogel spacers to improve rectal sparing during RT were not included, given their relative novelty and lack of randomized data comparing surgical and radiotherapeutic outcomes. Searches of published abstracts were also included in the formation of the manuscript when full articles were not available. Finally, the manuscript and reference list were evaluated and approved by all authors for inclusion in the current publication.

## Technical Approaches for Surgery and Radiation

In general, there are two common approaches to RP, one which employs a retropubic approach, in which the prostate is removed through an incision in the wall of the abdomen, and the other a perineal approach, in which the incision is made in the area between the scrotum and anus<sup>45</sup> (Figure 1). Retropubic prostatectomy was considered the gold standard since the early 1980s due to the ability to access and remove pelvic lymph nodes, as well as spare cavernosal nerves. The dorsal vein complex is at risk, however, and blood loss requiring transfusions has been shown to be a risk of this approach.<sup>46</sup> Since many patients at low risk for metastasis do not require extensive pelvic lymph node dissection, a perineal prostatectomy is an alternative approach and often causes less blood loss by avoiding the dorsal vein complex.<sup>47</sup> Regarding robotic prostatectomy, studies have shown lower estimated blood loss, shorter hospital stays, a lower incidence of bladder neck contractures/anastomotic strictures, and lower intraoperative adverse event.<sup>48</sup> However, there is a lack of randomized, long-term studies that compare functional and oncologic outcomes between open and robotic approaches. Modern robotic techniques (e.g., NeuroSAFE) continue to evolve, including intraoperative fresh-frozen section analysis of prostate margins to assess

and optimize oncologic resection while maintaining functional outcomes, with randomized trials underway.<sup>49</sup> Overall, most patients who opt for definitive management with prostatectomy can initially avoid androgen deprivation therapy and its associated effects on quality of life (QOL).

With regard to radiation, there are multiple techniques including XRT and BT. Dose escalation to 74–81 Gy has been shown to improve biochemical failure-free survival over lower doses; however, no overall survival benefit has been shown with these increasing doses over lower doses (~70 Gy).<sup>8,50–53</sup> Hypofractionation, which typically uses 60–70 Gy over a shorter time interval, has demonstrated noninferiority to standard fractionation for low, intermediate, and high-risk disease; SBRT, a form of ultra-hypofractionated RT using image guidance and highly conformal techniques, has appeared safe at currently available follow-up and has allowed select patients to finish radiotherapy in 2 weeks.<sup>54</sup> Treatment to the prostate in the definitive setting is delivered to the organ with an additional 5–10 mm margin to account for organ motion or setup uncertainties, with the extent of coverage of the seminal vesicles informed by risk group and several intensity-modulated radiotherapy protocols available to guide planning.<sup>55</sup> Surrounding organs, such as the bladder, rectum, penile bulb, and bilateral femora, are delineated during planning as they receive radiation dose during treatment.<sup>56</sup> In the adjuvant and salvage setting, the prostate fossa is typically defined as at least 2 cm above the pubic symphysis to the top of the penile bulb, including surgical clips and seminal vesicle remnants if involvement is detected, with an additional 8–15 mm margin added due to setup uncertainty and movement.<sup>57</sup> The decision to treat lymph nodes significantly affects the anticipated exposure to the rectum and surrounding organs, as does the amount of margin necessary in the setting of chosen technique and image guidance. Rectal spacers are often used to mitigate short and late-term side effects of radiation therapy,<sup>58</sup> though these techniques have not yet been reflected in randomized data comparing the quality of life following surgery versus radiation.

## Limited Conclusions from Retrospective Observational Data

The reference standard in determining the impact any treatment modality has on an individual patient is the use of patient-reported outcomes (PROs), as they represent the



patients' perspective on how their quality of life has changed in contrast to physician-graded toxicity.<sup>59</sup> Reportable tools and assessments have been developed and increasingly deployed across observational and prospective research.<sup>60</sup> Given the sample sizes and amount of follow-up required to measure differences in both frequent and infrequent morbidity endpoints, it has been tempting to use prostate cancer registries to answer questions regarding the differential incidence of various toxicities between approaches using upfront RP and RT. These cancer registries have tracked different levels of detail concerning treatment, with several important features such as ADT use, RT dose, and radiation technique inconsistently tracked and reported.<sup>61</sup> Moreover, the use of these registries has more categorically been challenged by data suggesting that the systematic concordance between hazard ratios generated from observational studies and corresponding randomized controlled trials is little better than if left to chance.<sup>62</sup>

Despite these caveats, multiple efforts have attempted to leverage large sample size and registry data to answer quality of life questions following prostate cancer treatment.<sup>63–66</sup> The Prostate Cancer Outcomes Study utilized six Surveillance, Epidemiology and End Results registries to recruit 3533 men, 1655 of whom had surgery or radiotherapy for localized disease within a year of diagnosis with follow-up surveys at 2 and 5 years.<sup>63</sup> Men following surgery demonstrated more urinary incontinence and erectile dysfunction, while those receiving radiotherapy predominantly demonstrated GI symptoms including bowel urgency. These symptoms were noted at the early time points of 2 and 5 years, though all differences save for bowel symptoms were insignificant by year 15. Most of these men notably received an older generation of radiation therapy, with inconsistent utilization of ADT, though more modern data have been utilized to replicate these findings.<sup>64,65</sup>

## Quality of Life Outcomes from Randomized Data and Prospective Cohort Studies

Prospective randomized controlled trials (PRTs) are considered by many as the reference standard for clinical studies as they allow for equal distribution of both measured and unmeasured covariates across strata of control and exposure groups, create a baseline timepoint for cohort evaluation and lend to easy statistical analysis. It

has become increasingly important to also assess functional outcomes when designing and conducting clinical trials in men with prostate cancer due to the improved understanding of converging oncologic outcomes with surgery and radiation. Accordingly, it would reason that PROs incorporated into prospective randomized studies of men treated for prostate cancer would serve as the highest level of evidence to directly compare treatment-related toxicity and QOL. Despite this, there remains a paucity of PROs obtained from RCT's to help guide physicians and patients on expected toxicities when selecting an appropriate treatment approach in the setting of multidisciplinary care.

The quality of life companion article of men enrolled in the Prostate Testing for Cancer and Treatment ( ProtecT ) trial may provide the best prospective QOL data in men with localized prostate cancer following treatment with one of the most commonly used methods: surgery, radiotherapy or active monitoring.<sup>67</sup> Briefly, the ProtecT study was a multicenter, randomized clinical trial of men with screening-detected prostate cancer who were randomized in a 1:1:1 fashion to either radical prostatectomy, active monitoring or radiotherapy with 4 months of ADT.<sup>4</sup> In all, 545 men were randomized to active monitoring, 553 men to radical prostatectomy and 545 men to radiotherapy + ADT. After 10 years of follow-up, the authors noted no difference in PCM, though the measured PCM remained low in all cohorts, with only 17 prostate cancer-specific deaths.<sup>4</sup> It is important to note that most men enrolled in the ProtecT study had low-risk disease and further extrapolation of this study to cohorts of men with high-risk disease is cautioned, a risk category that will likely need to wait for the results of SPCG-15 for randomized data.<sup>68</sup>

In the ProtecT QOL study by Donovan et al, 1643 men enrolled on ProtecT completed validated questionnaires before diagnosis, at 6 and 12 months after randomization, and annually thereafter.<sup>67</sup> The companion study was designed to provide a direct comparison of the QOL of men treated uniformly with either radiotherapy/ADT, radical prostatectomy, or active monitoring. The study included validated measures that assessed multiple domains including urinary, bowel, sexual function, and specific effects on quality of life, anxiety, depression and general health. The published report included 5 years of follow-up data on cancer-related quality of life and 6 years of follow-up data on additional endpoints. The authors analyzed the data according to the intention-to-treat principle based upon patient randomization into the treatment

groups of the ProtecT trial. Overall, radical prostatectomy was associated with worse outcomes in erectile dysfunction and urinary incontinence compared with radiotherapy and 4 months of ADT. Conversely, radiotherapy and ADT were associated with significantly more bowel toxicity (Table 2). Importantly, when assessing the entire cohort, no significant differences were observed among any treatment group in general health-related, cancer-related quality of life, depression or anxiety.<sup>67</sup> Despite equivalence in global health-related quality of life between treatment modalities, the study does demonstrate that toxicity profiles between radiotherapy and radical prostatectomy are different. These data are useful when discussing with patients. Overall, radiotherapy is more associated with worsened bowel symptoms while prostatectomy is associated with worsening of urinary incontinence and erectile dysfunction. To magnify this association, the authors report that compared to the active monitoring group the number needed to treat (NNT) to cause a single additional case of erectile dysfunction at 2 years is 4 with radical prostatectomy and 8 with radiotherapy, and the NNT to cause a single additional case of urinary incontinence at 2 years is 5 for RP and 143 for RT. However, as follow-up continued to 6 years the authors demonstrate that urinary and sexual function had stabilized in the radiotherapy group after improving for 2–3 years, while urinary and sexual function declined over this time period in the active monitoring group. As such, with this additional follow-up, the authors conclude that men treated with either active monitoring or radiotherapy with ADT had similar QOL with respect to sexual function and urinary incontinence, but these scores remained worse in men treated with prostatectomy.

It is important to note that the ProtecT study used modern approaches to surgery and thus may not be biased by older surgical procedures. The authors note that the majority of the 545 men randomized to radical prostatectomy underwent an open retropubic, nerve-sparing procedure. This nerve-sparing approach would be expected to reduce the rates of toxicities such as erectile dysfunction. In the radiation arm, patients were treated with modern dose-escalated prescriptions to 7400 cGy in 37 fractions using three-dimensional conformal radiotherapy. While the dose in this cohort reflects modern prescribing, newer techniques such as intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) are now more routinely used as they are associated with fewer toxicities compared with 3D conformal radiation.<sup>69</sup>

Despite this, the QOL data from the ProtecT study provide high-quality evidence regarding the impact of modern treatments for men with clinically localized prostate cancer and can be used to guide physicians and patients when considering treatment recommendations.

Another PRT comparing surgery vs radiotherapy with PROs was conducted by Lennernas et al and included men with locally advanced high-risk prostate cancer.<sup>70</sup> This study conducted in Sweden between 1996 and 2001 included 89 men and randomized them 1:1 to either radical prostatectomy or radiotherapy consisting of 50 Gy external beam radiotherapy with high-dose-rate brachytherapy delivered in 2 separate fractions of 10 Gy each. All men in the trial were also treated with 6 months of neoadjuvant total androgen blockade. The primary outcome was the difference in health-related quality of life (HRQoL) using PROs. The study assessed self-reported HRQoL and symptoms including urinary, bowel, and sexual function prior to randomization and at 12 and 24 months following randomization.<sup>70</sup> The authors report that no discernible differences in HRQoL or complications were demonstrated between the two treatment groups. One unique aspect of the study is that all men were treated with total androgen blockade. This allows for a better comparison between the two treatment modalities of radiotherapy and surgery without ADT confounding the radiotherapy arm. It also compares what has been described as maximal radiotherapy with combination XRT and BT. Combination XRT and BT have been shown to be associated with significantly more toxicity compared with XRT alone in prospective studies.<sup>20</sup> Given that all men were treated with ADT and the radiotherapy arm received maximal radiotherapy, this study provides data that even in high-risk men treated aggressively, HRQoL as measured using PROs was similar between treatment arms. This study is limited by the small sample size and the nonconventional XRT dose given in the radiation arm but still provides valuable information using PROs from an RCT.

Another (pseudo)randomized study that published PROs is the American College of Surgeons Oncology Group Phase III Surgical Prostatectomy versus Interstitial Radiation Intervention Trial (ACOSOG SPIRIT) by Crook et al.<sup>71</sup> This study compared RP with BT given definitively as monotherapy. The trial was initially designed as a randomized study but after slow accrual, the protocol was amended to allow patients to choose or be randomized to either RP or BT. Overall, the trial was terminated early due to poor accrual but the authors report on HRQoL at 5

**Table 2** Key Prospective Studies Examining Quality of Life in Prostate Cancer

Author (Year)	Exposure	Erectile Dysfunction	Urinary Incontinence	Urinary Voiding Symptoms	Bowel Symptoms	HRQoL (Overall)	Study Limitations	Study Strengths
Randomized Trials								
Donovan <sup>67</sup> (2016)	1. RP 2. XRT + 4 months ADT 3. Active Monitoring	Worse in RP group at 6 months post-treatment and all time points	Worse in RP arm at 6-months post-treatment and all time points	Worse in the RT + ADT arm at 6 months with return to near baseline levels	Worse in RT + ADT arm at all-time points	Equivalent	Homogenous population	Large Series, Radiation arm included ADT, Modern techniques for surgery and radiation
Lennermäs <sup>70</sup> (2015)	1. RP + ADT 2. XRT + BT Boost + ADT	Decreased in both groups, but equivalent	Equivalent	Equivalent	Equivalent	Equivalent across both groups	Small series (n=89), closed early due to low accrual	Entire cohort received ADT
Crook <sup>71</sup> (2010)	1. RP 2. BT monotherapy	Worse after RP	Worse after RP	Equivalent	Equivalent	Not Reported	Small series, closed early due to poor accrual, only 19% of patients randomized	Outcome data at 5 years
Giberti <sup>72</sup> (2009)	1. RP 2. BT monotherapy	Worse in RP at 2 and 5 years	Equivalent	Greater in BT arm on short follow-up, equivalent long term	Worse in BT arm on short-term follow-up, equivalent long-term	Equivalent	Only used Brachytherapy,	Validated metric, Long term follow-up (15) years
Morris <sup>20</sup> (2016) Rodda <sup>73</sup> (2017)	1. XRT + ADT + XRT boost 2. XRT + ADT + LDR BT boost	Similar between arms	Worse with LDR Boost	Worse with LDR Boost	Equivalent	Not Reported	Only compared radiation techniques	Large study with long term follow-up

(Continued)

Table 2 (Continued).

Author (Year)	Exposure	Erectile Dysfunction	Urinary Incontinence	Urinary Voiding Symptoms	Bowel Symptoms	HRQoL (Overall)	Study Limitations	Study Strengths
Prospective Studies								
Hoffman <sup>74</sup> (2020)	1. Active Surveillance 2. RP 3. XRT 4. BT 5. XRT + ADT	Worse in RP and BT arm	Worse in RP and BT	Worse in BT	Worse in XRT + ADT at 1 year	Equivalent at 5 years in domains: Physical function, emotional well-being, and energy	Non-randomized, population-based cohort study	Large study, 5-year follow-up

Abbreviations: ADT, androgen deprivation therapy; BT, brachytherapy; RP, radical prostatectomy; RT, radiation therapy; XRT, external beam radiation therapy.

years in patients enrolled on the trial. Overall, 168 men were eligible for the toxicity analysis. In the entire cohort, 60.7% of men had BT (9.5% randomly assigned) and 39.3% of men had an RP (9.5% randomly assigned). Five years after treatment all men were considered for HRQoL evaluation using the cancer-specific 50-item Expanded Prostate Cancer Index Composite, the Short Form 12 Physical Component Score, and the Short Form 12 Mental Component Score. The overall response rate was 88.4%. With a median follow-up of 5.2 years, the authors report no differences between RP and BT in bowel or hormonal domains. However, men treated with BT scored better in urinary (91.8 v 88.1;  $p=0.02$ ) and sexual (52.5 v 39.2;  $p=0.001$ ) domains as well as in patient satisfaction (93.6 v 76.9;  $P<0.001$ ).<sup>71</sup> This study is limited in its small sample size and largely non-random allocation (only 19% of patients were randomly assigned) but provides evidence that brachytherapy as monotherapy had fewer adverse effects on HRQoL compared with prostatectomy.

In a similar study, Giberti et al randomized 200 patients to either radical retropubic prostatectomy or brachytherapy as monotherapy and reported on oncological and functional outcomes.<sup>72</sup> Men randomized to surgery underwent bilateral nerve-sparing retropubic RP and standard lymph node dissection and men randomized to BT received low-dose rate brachytherapy using I-125 seeds with a prescribed dose of D90 > 140 Gy. All men received questionnaires including the International Prostate Symptom Score (IPSS), International Index of Erectile Function (IIEF), and the EORTC-QLQ-C30/PR25. Patients enrolled in the study completed questionnaires before treatment as well as every 3 months for the first year, every 6 months for the second year, and then annually. In this study, the authors report that RP was associated with worse erectile function while BT was associated with worse urinary voiding symptoms and bowel symptoms. Unlike the previously discussed studies, the authors found no difference in rates of urinary incontinence between study arms. Finally, as demonstrated in several other PRTs with PROs the authors report equivalent HRQoL between the treatment arms.<sup>72</sup>

Although not a trial of radiation compared with prostatectomy, the Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT) trial was a PRT of men with localized prostate cancer randomized to two different radiation techniques.<sup>20</sup> The study enrolled 398 men all of whom



received 12 months of neoadjuvant ADT followed by XRT to the prostate and elective nodes to a total dose of 46 Gy. Men were randomized into one of the two radiation boost arms: a standard dose-escalated XRT boost of an additional 32 Gy to a total of 78 Gy, or an LDR brachytherapy implant. The authors conclude that with 9 years of follow-up patients treated with an LDR brachytherapy implant had improved biochemical progression-free survival. However, compared with men who only received an XRT boost, those who underwent LDR brachytherapy had worse GU and GI toxicity as graded using the modified Late Effects of Normal Tissue – Somatic, Objective, Management, Analytic (LENT-SOMA) scale.<sup>73</sup> Although not an RCT between surgery and radiotherapy this study provides evidence that XRT with ADT combined with an LDR brachytherapy procedure has greater toxicity compared with the more commonly used approach of ADT with dose-escalated external beam radiotherapy.

A recently published prospective cohort study by Hoffman et al detailed the QOL impact of 1386 men with favorable-risk localized prostate cancer treated with either active surveillance (n=363), nerve-sparing prostatectomy (n=675), XRT alone (n=261) or low-dose rate brachytherapy (n=87) and in men with unfavorable-risk localized prostate cancer treated with RP (n=402) or XRT + ADT (n=217).<sup>74</sup> Patients reported their function using the 26-item Expanded Prostate Index Composite 5 years after completing treatment. Among men with favorable-risk disease, nerve-sparing prostatectomy was associated with worse urinary continence at 5 years and sexual function at 3 years compared with active surveillance. XRT was not associated with worse bowel, urinary or sexual side effects compared with active surveillance at any point during 5 years after treatment. In the unfavorable risk subset, XRT + ADT was associated with worse bowel function at 1 year, but better sexual function and incontinence compared with RP at each time point through 5 years. Overall, the results of the Hoffman analysis provide evidence that XRT has a more favorable toxicity profile compared with RP even when ADT is added in the unfavorable subgroup. Fortunately, none of the treatment groups reported meaningful declines in the HRQOL domains of physical function, emotional well-being, and energy/fatigue scores.

As discussed, ADT is often added to XRT or BT in unfavorable intermediate-risk and high-risk patient populations. In addition to the toxicities caused by radiotherapy, ADT introduces additional side effects. Several studies

have shown that ADT independent of the effects of radiotherapy contributes to worse sexual function.<sup>75,76</sup> In a study by Gay et al the addition of neoadjuvant ADT to XRT or BT was associated with worse QOL. Specifically, the authors demonstrate that men on ADT had a decreased ability to reach orgasm, had decreased quality of erections and decreased sexual function.<sup>77</sup> ADT also has metabolic effects and can lead to increased weight gain and loss of muscle mass. Unlike other toxicities associated with prostate cancer treatment, the side effects attributable to ADT are often only transient and resolve after discontinuation and normalization of testosterone levels.

Finally, in men who undergo RP but require post-operative radiotherapy either in the adjuvant or salvage setting the addition of radiotherapy after prostatectomy has been shown to worsen QOL. Jenkins et al studied 106 men with PCa receiving post-prostatectomy radiotherapy and assessed the QOL impact of radiotherapy using the Expanded Prostate Cancer Index Composite (EPIC). The authors demonstrate that post-prostatectomy radiotherapy worsened urinary QOL with the most significant decline noted in urinary incontinence.<sup>78</sup> Other studies of post-prostatectomy radiotherapy show only temporary worsening of symptoms in urinary, sexual and bowel domains.<sup>79</sup> Overall, studies seem to indicate a worse urinary function in men who require post-prostatectomy radiotherapy.<sup>80</sup> Given this information, it is important to consider these implications when counseling men with high risk, high volume disease (Gleason score 9–10) who would most likely require adjuvant/salvage radiotherapy following RP. In this setting, men may wish to consider definitive XRT + ADT and forgo RP given the high chances of requiring additional radiotherapy and the negative QOL impacts demonstrated in men receiving both modalities of treatment.

## Managing Toxicities Associated with Prostate Cancer Treatments

Given how successful treatment generally is for localized prostate cancer, managing the adverse effects associated with the various available treatment strategies is of paramount importance in order to maximize patient quality-of-life. For example, it is well known that one of the most bothersome toxicities associated with a surgical approach to prostate cancer treatment is urinary incontinence, with the risk of incontinence being highly dependent on both age and surgical technique.<sup>81</sup> Multiple strategies to aid

men to recover urinary control have been investigated, including both procedural and non-procedural techniques. For example, placement of artificial urinary sphincters has been shown to be a viable option, with the caveat that late complications may occur which may require further procedural intervention to remove the device.<sup>82</sup> In addition, transobturator sling suspension via placement of transobturator tape has also been studied, resulting in a significant rate of both complete cure of incontinence and decreased pad usage.<sup>83</sup> Finally, behavioral training with biofeedback seems to be effective specifically for stress and urge incontinence, but less so with patients who experience continual leakage of urine following a prostatectomy.<sup>84</sup>

While incontinence following radiation treatment for prostate cancer is a rare side effect, radiation may instead cause hemorrhagic cystitis and radiation proctitis, both of which also negatively impact patient quality of life. Radiation cystitis can manifest itself both in the acute post-treatment time period and multiple months to years following completion of radiation treatment, and can vary significantly in severity from a mild bleed up to significant hemorrhage; as such, management strategies differ but include cystoscopy with electrocoagulation of bleeding areas, injection of botulinum toxin into the bladder wall, and instillation of compounds such as formalin or prostaglandins into the bladder itself.<sup>85</sup> For radiation proctitis, direct instillation of formalin during a sigmoidoscopy has shown to be effective and often results in immediate resolution of symptoms.<sup>86,87</sup> Alternatively, argon plasma coagulation, also performed during a flexible sigmoidoscopy, has also been demonstrated to be effective in both reducing blood transfusion requirements related to radiation proctitis and improving other aspects of bowel function such as resolving rectal urgency and stool frequency.<sup>88</sup> Radiofrequency ablation is an option for those whose symptoms do not resolve with first or second-line interventions as well.<sup>89</sup> For those who prefer a less invasive therapy, short-chain fatty acid enemas were superior to placebo in a prospective, randomized double-blind trial examining the rapidity of healing of radiation proctitis.<sup>90</sup> Finally, hyperbaric oxygen has been shown to be an effective treatment strategy for both patient complaints of hematuria related to radiation cystitis and rectal bleeding or irritation from radiation proctitis following radiation treatment for prostate cancer, but the use of this technique is generally reserved after other lines of therapy have been ineffective.<sup>91,92</sup>

For many men undergoing treatment for prostate cancer, maintenance of sexual function is an extremely important consideration and component of their quality of life; unfortunately, sexual dysfunction is a common adverse effect of both RT and RP, with similar rates for both therapies (particularly now that surgical techniques have improved such that nerve-sparing approaches are possible for localized disease). Complicating studies on this subject is the fact that with the exception of a recently validated standardized questionnaire, the International Index of Erectile Function (IIEF), defining terms such as “potency,” “satisfactory sexual function,” “sexual interest,” and “libido,” among others, is dependent on individual interpretation.<sup>93</sup> The first-line treatment for erectile dysfunction is generally an oral phosphodiesterase type 5 (PDE5) inhibitor, although specific dosages and frequencies of administration vary.<sup>94</sup> In fact, prophylactic sildenafil citrate initiated before radiation therapy for prostate cancer and given continuously with the intent of preserving erectile function until 6 months following completion of radiation therapy was demonstrated to improve long-term sexual outcomes.<sup>95</sup> Should patients not respond to oral PDE5 agents, patients are generally offered penile injections, penile implants, or vacuum erection devices.<sup>96–98</sup> Less invasive options such as exercise therapy (with moderate to high intensity aerobic and resistance training exercises) have also been shown to be effective, even though they do not directly act on sexual organs, as sexual function is intimately interwoven with mental health and well-being.<sup>99</sup> Finally, clear, constructive communication between patients and their partners has been consistently shown to be one of the most important factors in helping patients cope with sexual problems following prostate cancer treatment.<sup>100</sup>

Perhaps most importantly, comprehensive patient counseling of the risks and benefits of each potential treatment option is appropriate in men with localized prostate cancer. Many tools are available to aid this process; for example, nomograms have been developed to predict both acute and long-term rectal toxicity associated with radiation therapy<sup>101–103</sup> as well as urinary adverse events.<sup>104</sup> Involvement of a multidisciplinary team of healthcare providers is essential such that the patient is able to appreciate all available options for treatment, and ultimately, although a consensus recommendation can be made based on patient characteristics and/or disease involvement, patient participation with an informed final decision is the most critical component to the management of patient expectations regarding toxicity.<sup>105–107</sup>

## Conclusion

As discussed, there is a paucity of prospective randomized data with PRO metrics for men treated with localized prostate cancer. Based on the current review it appears that prostatectomy is associated with higher rates of urinary incontinence and erectile dysfunction compared to radiotherapy. Unlike surgery, radiotherapy appears to be associated with worsening bowel function. However, despite these differences, prospective evaluation seems to indicate that global HRQoL does not differ in men by treatment modality. Thus, an individualized discussion that compares and contrasts different toxicity profiles of each treatment modality may be the best approach clinically to encourage patient engagement in the shared medical decision-making process. There are myriad tools and interventions, both procedural and non-procedural, available to address the sequelae of an upfront RP or RT-based approach. In the future, we believe that all men with prostate cancer should have an informed discussion in the setting of a multi-disciplinary setting to hear of all of the information available before deciding on a treatment approach.

## Acknowledgments

The authors would like to thank Herbert Colunga for artistic contributions related to [Figure 1](#).

## Disclosure

The authors report no conflicts of interest for this work.

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