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Survival and Complications Following Surgery and Radiation for Localized Prostate Cancer: An International Collaborative Review

Christopher J.D. Wallis[1,2], Adam Glaser[3], Jim C. Hu[4], Hartwig Huland[5], Nathan Lawrentschuk[6,7,8], Daniel Moon[8,9,10], Declan G. Murphy[8,10], Paul L. Nguyen[11], Matthew J. Resnick[12,13], Robert K. Nam[1,2]

Author affiliations:
[1]Division of Urology, Department of Surgery, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada
[2]Institute of Health Policy, Management, & Evaluation, University of Toronto, Toronto, ON, Canada
[3]Leeds Institute of Cancer and Pathology, University of Leeds, Leeds, UK
[4]Department of Urology, Weill Cornell Medicine, NY, NY, USA
[5]Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany
[6]Department of Surgery, University of Melbourne, Austin Health, Melbourne, Australia
[7]Olivia Newton-John Cancer Research Institute, Austin Health, Melbourne, Australia
[8]Division of Cancer Surgery, Peter MacCallum Cancer Centre, Melbourne, Australia
[9]Central Clinical School, Monash University, Victoria, Australia
[10]The Epworth Prostate Centre, Epworth Hospital, Richmond, Victoria, Australia
[11]Department of Radiation Oncology, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA, USA
[12]Department of Urologic Surgery, Vanderbilt University Medical Center, Nashville, TN, USA
[13]Geriatric Research, Education, and Clinical Center, Tennessee Valley VA Health Care System, Nashville, TN, USA

Address for Correspondence:
Dr. Robert Nam
Room MG-406 2075 Bayview Ave.
Toronto, Ontario, Canada M4N 3M5
Phone: (416) 480-5075 FAX: (416) 480-6934
Email: Robert.nam@utoronto.ca

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ABSTRACT

Background: Evaluation of treatment options for localized prostate cancer continues to be among the highest priorities for comparative effectiveness research. Surgery and radiotherapy are the two most commonly used interventions.

Objective: To provide a critical narrative review of the evidence surrounding the comparative effectiveness and harms of surgery and radiotherapy in the treatment of localized prostate cancer.

Evidence acquisition: A collaborative critical narrative review of the literature was conducted.

Evidence synthesis: Evidence to clearly guide treatment choice in prostate cancer remains insufficient. Randomized trials are underpowered for clinically-meaningful endpoints and have demonstrated no difference in overall or prostate cancer-specific survival. Observational studies have consistently demonstrated an absolute survival benefit for men treated with radical prostatectomy, but are limited by selection bias and residual confounding errors. Surgery and radiotherapy are associated with comparable health-related quality of life following treatment in three randomized trials. Randomized data regarding urinary, erectile, and bowel function show few long-term (>5 year) differences though short term continence and erectile function were worse following surgery and short term urinary bother and bowel function were worse following radiotherapy. There has been recent recognition of other complications which may significantly affect the life trajectory of those undergoing prostate cancer treatment. Of these, hospitalizations, the need for urologic, recto-anal and other major surgical procedures, and secondary cancers are more common among men treated with radiotherapy. Androgen deprivation therapy, frequently co-administered with radiotherapy, may additionally contribute to treatment-related morbidity. Technological innovation in surgery and radiotherapy have shown inconsistent oncologic and functional benefits.

Conclusions: Due to underpowered randomized control studies and the selection biases inherent from observational studies, the question of which treatment provides better cancer control cannot be definitively answered now or in the near future. Complications following prostate cancer treatment are relatively common regardless of treatment approach. These include the commonly identified issues of urinary incontinence and erectile dysfunction and others including hospitalizations and invasive procedures to manage complications, and secondary malignancies. Whole population-based outcome studies, rather than clinical trial data, will be necessary to enable comprehensive understanding of the relative benefits and risks of each therapeutic approach.

Patient summary: Surgery and radiotherapy are the most common interventions for men diagnosed with prostate cancer. Comparisons of survival after these treatments are limited by various flaws in the relevant studies. Complications are common regardless of treatment approach.

1. INTRODUCTION

For three decades, management options for patients with clinically-localized prostate cancer (PCa) have remained the same – surgery, radiotherapy, and observation. Many men, particularly those who are older or have low-risk PCa, will not benefit from active intervention[1]. For men with a long life expectancy (>10 years), treatment is recommended for those with intermediate or high-risk PCa[2]. Both surgery and radiotherapy (now usually in combination with androgen deprivation therapy, ADT) have been used in the treatment of PCa for over 100 years. While other treatments such as high intensity frequency ultrasound (HIFU) and cryotherapy are gaining prominence, the volume of evidence surrounding intermediate- and long-term outcomes remains insufficient to guide treatment decision-making. Accordingly, these treatments are not routinely recommended in clinical practice guidelines[2].

Without significant supportive evidence, surgery and radiotherapy (generally in combination with ADT) have been advocated as having similar oncologic efficacy. Thus, treatment counselling and decision making has been complex and predominately centred on risks of urinary incontinence and erectile dysfunction and other radiation-specific side-effects (and increasingly side effects of ADT as we have become aware of them in the past decade). The importance of localized PCa management is highlighted by its selection by the Institute of Medicine as one of the top 25 priorities for comparative effectiveness research[3]. In the past few years, a significant body of literature has emerged assessing survival and complications following treatment of localized PCa. Thus, in this collaborative narrative review, we summarize historical and contemporary data evaluating survival outcomes and complications following radical prostatectomy and radiotherapy in the treatment of clinically-localized PCa, including consideration for the role and toxicity of ADT co-administered in most modern radiotherapy regimes.

2. EVIDENCE ACQUISITION

MEDLINE was systematically searched from inception until December 2016 using the following terms: “radical prostatectomy”, “radiotherapy”, “brachytherapy”, “survival”, “complications”, and “outcomes” along with free-text, related, derivative, and exploded terms. The lead author compiled a proposed bibliography and manuscript framework which was iteratively revised by all co-authors. Following agreement on manuscript structure, the first and senior authors drafted this narrative review that was critically revised by co-authors. The final manuscript represents the consensus of the authors.

3. EVIDENCE SYNTHESIS

3.1 Oncologic outcomes in prostate cancer research

Many cancer-related outcomes have been used in comparative effectiveness studies of PCa treatments including biochemical recurrence, clinical recurrence, metastasis, PCa-specific mortality and overall mortality. All-cause (overall) mortality is the most reliable endpoint of any oncology study and, according to the United States Food and Drug Administration, is the preferred endpoint due to its precision and lack of ascertainment bias[4]. Previous work has shown that PCa may be reliably ascertained as a cause of death from administrative records[5]. Thus, PCa-specific survival is an alternative outcome that may more directly assess the oncologic efficacy of PCa therapies.

Biochemical recurrence (BCR) is the most commonly used outcome in PCa treatment efficacy studies as it develops relatively early following treatment[6]. While BCR is an important clinical event, most notably as it triggers further therapy with significant costs and quality of life

detriments[7-9], it is limited as a meaningful research outcome. First, approximately 10% of men with BCR will develop clinical progression[10], and less than 5% at 5 years will ultimately die of disease[10]. Thus, BCR is a poor surrogate measure for survival. Second, there exist innumerable definitions of biochemical recurrence (BCR). A systematic review of the literature in 2007 identified 53 different definitions for BCR following radical prostatectomy and 99 different definitions for BCR following radiotherapy[11], making it difficult to compare outcomes between studies. Finally, given the intrinsically different definitions of BCR for patients treated initially with surgery and radiotherapy, the use of BCR to compare outcomes following treatment with the two modalities is inherently problematic. Both the Phoenix criterion and ASTRO criteria as a definition of BCR systematically overestimate biochemical-recurrence free survival for patients following radical prostatectomy[12]. Further, Lee et al. showed that among men with comparable five-year risks of BCR, those treated with radiotherapy as compared to surgery had significantly increased risk of PCa-specific mortality[13]. Thus, while clinically meaningful, BCR should not be used to compare oncologic efficacy of PCa treatments and this review focuses on survival outcomes.

3.1.1 Randomized survival data

Radical prostatectomy is the only treatment shown in a randomized controlled trial to improve overall and cancer-specific survival for patients with localized PCa, compared to watchful waiting[14]. In the Scandinavian Prostate Cancer Group Trial #4 (SPCG-4), Bill-Axelson et al. randomized 695 men with early clinically-detected PCa to radical prostatectomy or watchful waiting[14]. In addition to a survival benefit, surgery reduced the risk of metastasis[14]. These benefits were not confirmed in a similar study (Prostate Cancer

Intervention versus Observation Trial, PIVOT)[15], though this study is limited by inclusion of proportionally more men with low-risk disease and more men with significant comorbidities and shorter follow-up (median 10 years). In the SPCG-4 trial, the benefit of surgery has continued to increase as ongoing follow-up has accrued.

Two older randomized trials compared survival outcomes following radical prostatectomy and radiotherapy. The first was conducted by the Uro-Oncology research group in the pre-PSA era[16] and the second by the Japanese Study Group for Locally Advanced Prostate Cancer more recently[16]. Both demonstrated improved outcomes in surgically treated patients, however due to methodologic limitations (including insufficient follow-up) and the evolution of medical practice (including stage migration due to the introduction of PSA screening), neither of these studies have influenced current clinical practice.

Recently, the Prostate testing for cancer and Treatment (ProtecT) trial reported survival outcomes among 1643 patients randomized to active monitoring, radical prostatectomy and radiotherapy[17]. The investigators found no significant difference in their primary outcome of PCa specific mortality (p=0.48) with eight attributable deaths in the monitoring group, five in the surgery group and four in the radiotherapy group[17]. Overall mortality rates were also comparable (p=0.87). Limitations of applying these data to clinical practice have previously been reported[18,19]. Most notably, there is a lack of statistical power, a fact recognized years before manuscript publication[20], due to a significant overestimation of predicted mortality rates at the time of study design. In addition, there is over-representation of patients with low-risk disease among the study cohort[20]. Based on these limitations, it is unlikely that meaningful comparisons of mortality for patients treated with surgery and radiotherapy will ever be made

from this cohort. Nonetheless, ProtecT identified a significant reduction in both clinical progression and metastatic disease among men receiving definitive therapy.

Among 89 patients with localized or locally-advanced PCa randomized to surgery or radiotherapy (EBRT + brachytherapy boost + ADT), Lennernas et al. recently reported no difference in overall or cancer specific mortality, though the authors correctly concluded that they were underpowered to assess survival outcomes[21].

3.1.2 Observational survival data

Considering the limitations among available randomized trials, a recent meta-analysis of observational studies compared overall and prostate-cancer specific mortality for patients treated with surgery and radiotherapy[22]. Utilizing pooled results of 95,791 patients for the outcome of overall mortality and 118,830 patients for PCa-specific mortality, patients treated with radiotherapy had a significantly increased risk of death (overall mortality: HR 1.63, 95% CI 1.54 – 1.73; PCa-specific mortality: HR 2.08, 95% CI 1.76 – 2.47). These findings were robust to subgroup and sensitivity analyses including PCa risk categorization, study accrual period, radiotherapy modality (EBRT or brachytherapy), duration of follow-up, and geographic region of study[22]. It is notable that a survival benefit was found even among patients with low-risk disease, likely reflecting a combination of the Will Rogers phenomenon[23] and residual confounding.

While observational data cannot account for unmeasured confounding in the manner of a randomized controlled trial, as others have highlighted[24,25], the included studies were deemed at low to moderate risk of bias using the Newcastle-Ottawa Scale, a validated measure recommended by the Cochrane Collaborative to evaluate observational studies[26]. In contrast,

another meta-analysis which downplayed differences in survival between surgery and radiotherapy[25] did not use a validated measure for bias assessment. Initially, the authors attempted to employ the GRADE criteria[27]. Rather than relying on this validated measure, they subsequently constructed a subjective reliability scale based on their "perceptions about the relative importance of each factor"[25]. The authors deemed single institutional studies to be of higher "reliability" than multi-institutional reports and penalized studies reporting on populations greater than 12,000 patients, even though these studies have greater external validity. Despite this, the authors demonstrated that radical prostatectomy was associated with improved overall and cancer-specific survival compared to radiotherapy.

There are many ways to account for selection biases, most principally confounding by indication, in observational studies including regression techniques, propensity-score approaches (including matching and weighting), and instrumental variable techniques. Many of the studies in the meta-analysis included all identifiably relevant patient and tumor characteristics in regression or propensity-score matched analyses[22]. While these approaches account for observed confounders, instrumental variable analyses may also account for unmeasured confounding. Using such an approach in patients with ≥ten-year predicted life expectancy, Sun et al. found improved survival among those treated with surgery compared to radiotherapy (HR 0.66, 95% CI 0.56 – 0.79)[28]. While instrumental variable analyses have been shown to provide less biases estimates of treatment effect[29], these techniques are unable to fully account for selection bias and consequently residual confounding remains[30]. Furthermore, there remain important statistical limitations with respect to their ability to determine differences in outcomes. To address such residual confounding, Cooperberg et al. performed an elegant sensitivity analysis in which Kattan scores were artificially increased for patients undergoing prostatectomy[31]. To

show that surgery was not better than radiation, there had to be an increase of more than 30 Kattan points which was considered unrealistic.

Other concerns with the meta-analysis of observational studies[22] include the relevance of the included treatments, given recent advances in radiotherapy. However, examining patients treated with dose-escalated IMRT (>81 Gy) compared to radical prostatectomy, Zelefsky et al. found comparable results[32]. Among patients with high grade PCa, Kishan et al. found no difference in overall survival between those treated surgically, those treated with EBRT and ADT, and those treated with EBRT, brachytherapy boost, and ADT[33]. While the authors found lower rates of metastasis among men receiving radiotherapy and ADT, this is confounded by short follow-up (<5 years) and the co-administration of ADT.

This meta-analysis represents Level 2a evidence, although the limitations to account for unmeasured confounding continue to be a problem for these studies [34]. Thus, despite a number of studies on this topic (Table 1), this remains an unresolved question.

3.2 Global health-related quality of life

A recent systematic review highlighted the importance of patient-derived health related quality of life assessment in the evaluation of treatment outcomes in patients with urologic cancers[35]. While specific patient-reported functional domains are of interest and more likely to reflect treatment-related mechanisms, global health-related quality of life (HRQoL) may be more meaningful, despite limitations due to the ceiling effect of these instruments. Three contemporary randomized controlled trials assessed patient-reported outcomes (PROs) including global HRQoL (Table 2). Among the ProtecT cohort, Donovan et al. demonstrated no differences in physical health, mental health, anxiety or depression among men treated with

surgery or radiotherapy[36]. Lennernas et al. and Gilberti et al. similarly found no difference in overall measures of health-related quality of life whether patients were treated with EBRT or brachytherapy, as compared to radical prostatectomy[21,37]. PCa treatment may also affect the quality of life of patients' spouses[38]. Further work, including the development of measures which overcome the ceiling effect, is urgently needed in this area.

3.3 Functional outcomes: "classic complications"

The best characterized and most frequently discussed complications of PCa treatment are urinary incontinence and erectile dysfunction. SPCG-4 demonstrated that radical prostatectomy increased rates of each of these complications, while decreasing rates of urinary obstruction, compared to watchful waiting[39]. Due to field effects of radiotherapy, both EBRT and brachytherapy significantly affect the bowel and rectal domains of HRQoL[40]. While most bowel effects are transient, a proportion persist for many years after treatment[40]. Typically, bowel symptoms are worse for patients undergoing EBRT than those receiving brachytherapy[41].

As with global HRQoL, three randomized controlled trials compare patient-reported functional outcomes for those treated with surgery and radiotherapy. In the ProtecT study, surgery was associated with increased rates of urinary incontinence and erectile dysfunction while radiotherapy had greater obstructive urinary symptoms and bowel symptoms[36]. Differences in urinary incontinence and erectile dysfunction between treatment modalities diminished with longer follow-up[36], in keeping with the observational findings of the Prostate Cancer Outcomes Study[42]. Lennernas et al. found no significant differences in urinary urgency, urinary incontinence, erectile dysfunction, sexual interest, or rectal bleeding between

men treated with surgery or radiotherapy[21]. They noted significant worsening in urinary incontinence, erectile dysfunction, and sexual interest over time in both groups. Gilberti et al. found that men treated with brachytherapy had worse urinary function at six and 12 months, worse bowel function at 6 months and better erectile function at six months compared to those treated surgically[37]. However, there were no significant differences in any functional outcome at five years.

There is a wealth of observational data examining patient-reported functional outcomes. Most notably, the Prostate Cancer Outcomes Study recruited 3533 men from six SEER registries[42] where 1655 patients with localized disease received surgery or radiotherapy treatment within 1 year of diagnosis and completed follow-up surveys beyond two years. At two and five years following treatment, men receiving surgery were more likely to report urinary incontinence and erectile dysfunction while those receiving radiotherapy were more likely to report bowel urgency and bother due to bowel symptoms[42]. By 15 years, all differences became non-significant, except for bowel symptoms which remained higher in men treated with radiotherapy[42]. Also, by 15 years, most men had developed erectile dysfunction[42]. More recent observational data have corroborated these findings among men treated with modern treatments, albeit with short (two and three year) follow-up[43,44].

Despite these data, a recent systematic review concluded there was insufficient data on symptomatic and quality-of-life outcomes following localized PCa treatment to provide meaningful treatment guidance[45]. In part, this is due to use of differing assessment measures. A recent Delphi consensus among patients, urologists and radiation oncologists sought to standardize the reporting of outcomes following localized PCa treatment[46]. They advocated using the Expanded Prostate Cancer Index Composite (EPIC-26) for assessment of patient-

reported outcomes, though numerous others were also endorsed. Data collection for ten years following treatment was recommended.

3.4 Functional outcomes: Novel complications

Complications related to PCa treatment may necessitate interventions including urologic procedures, rectal-anal procedures, and major surgery. These complications, including genitourinary or gastrointestinal bleeding, infection, and urinary obstruction, may also require planned or unplanned hospitalization[47]. Additionally, a further risk following radiotherapy is treatment-induced secondary malignancy.

In a large, population-based cohort of patients treated for non-metastatic PCa in Ontario, Canada, radiotherapy treatment was associated with an increased risk of hospitalization, rectal-anal procedures, major surgeries, and secondary cancers but lower risk of minimally-invasive urologic procedures, compared to surgery[47]. After propensity-score matching to account for baseline differences, patients receiving radiotherapy had increased long-term risk of all of these outcomes[48]. Validation in an independent cohort of patients from the United States showed that these complications frequently recur (mean 2.6 per patient) and continue for years following treatment[49,50]. Utilizing the same patient cohort but differing analytic methods, Williams et al. found no difference in treatment-related hospitalizations, though there was greater cost associated with treatment of patients who received radiotherapy[51].

While the use of post-operative radiotherapy contributed to increased complication rates, when taken on an intention-to-treat basis, the initial decision to begin therapy with surgery was associated with lower long-term risk of all procedural interventions and hospitalizations[9].

Complications arising from radiotherapy, the end result of which is chronic tissue ischaemia[52], have a profoundly different prognosis than those arising following surgery, which maintains the underlying tissue integrity. Radiotherapy-association complications are significantly more burdensome and often entail a much slower recovery, with impaired long-term function[53]. Most notably, urinary fistulae following prostate radiotherapy often require urinary diversion and are associated with significant morbidity[54].

In the Ontario cohort, patients treated with radiotherapy had a significantly increased risk of secondary cancers (standardized incidence rate (SIR) 2.0, 95% CI 1.7-2.3), driven by an excess of secondary cancers in men aged 40-65 at the time of radiotherapy (SIR 3.5, 95% CI 2.3-4.7)[47]. This finding has recently been supported by a meta-analysis comprising 21 studies and up to 555,873 patients[55] which found an increased risk of in-field secondary malignancies (bladder, rectal and colorectal cancers) but not of out-of-field malignancies among patients treated with radiotherapy, though the absolute risk was small (0-1.4 cases per 100 patients treated)[55].

Finally, there is growing evidence that radiotherapy may exert systemic effects. That radiotherapy has effects beyond the treatment field is relatively well-established[56]. A combination of systemic effects and local toxicity to the femur and pelvis may explain an observed association between radiotherapy and fracture risk which has been demonstrated among women with pelvic malignancies[57,58]. There is recent evidence demonstrating an independent association between radiotherapy and fracture risk in men treated for PCa[59], though others have not demonstrated this relationship[60]. Additionally, we recently observed an independent association between radiotherapy for clinically-localized PCa and the development

of coronary artery disease, myocardial infarction, and sudden cardiac death[59], although this requires further validation.

3.5 Effect of Androgen Deprivation Therapy

Androgen deprivation therapy (ADT) is often co-administered with radiotherapy based on evidence that it improves overall survival[61-63]. Thus, most radiation administered is in fact combination therapy. Long-term ADT (2 or 3 years) is recommended for patients with locally advanced disease rather than short-term therapy (6 months)[64]. However, among patients with localized disease, short-term ADT appears sufficient[65]. Nonetheless, both the ProtecT study and Lennernas et al. treated all patients receiving radiotherapy with ADT.

ADT is associated with detriments in bone health, cardiovascular disease, diabetes, sexual function, mental health, and cognition[66]. Further, ADT causes sexual dysfunction in more than 90% of treated men through decreased sexual interest (libido) and erectile function[67]. ADT has also been associated with decreases in penile length[68] and testicular size[69] which may be psychologically distressing and associated with treatment regret. A year following treatment, ADT was associated with significant impairments in HRQoL and with greater psychological distress than conservative management, while no differences were found between either surgery or radiotherapy and conservative management[70].

Most studies assessing ADT toxicity were conducted among men with advanced or metastatic disease and without consideration for local treatment. Recently, the adverse cardiovascular and skeletal-related effects of ADT have been demonstrated among patients with localized disease, undergoing definitive local treatment in an observational cohort[59]. Among patients with intermediate- and high-risk clinically-localized PCa in the DART 01/05

randomized trial, longer durations of ADT (24 months) were associated with an increased risk of cardiovascular events, compared to short durations (4 months)[71]. However, comparing treatment with ADT to no ADT, a recent meta-analysis of randomized trials showed no increased risk of cardiovascular death[72]. Adjuvant ADT may potentiate the bowel and sexual toxicity of radiotherapy (either EBRT or brachytherapy)[40,73] and the urinary and sexual toxicity following radical prostatectomy[74]. Further, adjuvant ADT has been associated with significant impairments in HRQoL[40]. Among patients undergoing radiotherapy, neoadjuvant ADT resulted in significant impairment in sexual- and vitality-related quality of life within 2 months of initiating ADT[75].

3.6 Evolving treatment modalities

3.6.1 Changes in surgical approach

Most survival and oncologic data for surgically treated patients presented in this manuscript are derived from patients treated with open retropubic radical prostatectomy. To our knowledge, there exists only one trial which randomized patients to open or robotic radical prostatectomy[76]. To date, only early perioperative outcomes are available. When assessed at 6 and 12 weeks following surgery, there were no significant differences in urinary or sexual function. Conclusions regarding positive margin rates could not be made.

Several population-based, observational cohort studies have compared open and robotic approaches. Assessing oncologic outcomes, robotic prostatectomy has been associated with a lower risk of positive surgical margins and of requiring additional cancer therapies[77,78] but no difference in overall or PCa-specific mortality[79]. Functionally, using patient-reported outcome

measures, O'Neil et al. found that patients treated robotically had better urinary and sexual function six months postoperatively, compared with those treated with open surgery[80]. The difference in sexual function persisted while differences in urinary function disappeared by 12 months. In contrast, Barry et al. found no difference in continence or sexual function based on operative technique[81].

Due to a combination of pro-innovation bias and changes in surgical training, it is likely that robotic prostatectomy will remain the preferred surgical approach. Centralization of care may lead to improved outcomes due to the established association between surgical volume and outcomes[82-84]. Further, operative advancements, including the use of a modified nerve-sparing technique[85] and neurovascular structure-adjacent frozen-section examination[86], may contribute.

3.6.2 Changes in radiotherapy delivery

Over the past two decades, intensity-modulated radiotherapy (IMRT) has largely supplanted 3-dimensional conformal radiotherapy (3D-CRT) for EBRT[87], and has been associated with less gastrointestinal toxicity, but comparable genitourinary toxicity[88,89]. Accompanying the transition to IMRT has been a trend towards dose-escalation, which has been shown to improve biochemical control and to reduce metastases in some randomized trials[90,91] although mortality appears comparable[88,92,93]. Early reports indicated that dose-escalation may be associated with increased gastrointestinal toxicity[92,94]; however, a recent review concluded that toxicity profiles were likely similar between dose-escalated and non-dose-escalated therapy[88]. Hypofractionation is associated with similar oncologic outcomes and toxicity, compared to conventional regimes[88,95,96]. Stereotactic body radiotherapy (SBRT)

combines dose-escalation and hypofractionation. While randomized comparisons to IMRT are ongoing, observational data suggest that SBRT has similar oncologic outcomes to IMRT[97] though SBRT but may be associated with increased erectile dysfunction[98], short-term genitourinary and gastrointestinal toxicity[99], and long-term genitourinary toxicity[99]. Finally, there has been interest in the use of proton EBRT though there is little evidence of improved oncologic or functional outcomes[100].

In addition to the described advances in the delivery of EBRT, there has been significant scientific interest in brachytherapy despite persistent and ongoing declines in its utilization[101-103]. The recently reported ASCENDE-RT trial demonstrated that the addition of brachytherapy boost to EBRT and ADT in men with intermediate- and high-risk disease was associated with improved biochemical control and comparable overall survival[104]. Brachytherapy boost was associated with increased genitourinary toxicity[105] and patient-reported worse overall health, sexual function, and urinary function[106].

4. CONCLUSIONS

Randomized trials assessing survival following surgery or radiotherapy in the treatment of clinically-localized PCa are significantly underpowered to address the question of relative superiority of surgery versus radiotherapy (and ADT) and are therefore limited in meaningfully informing clinical practice. Observational studies of hundreds of thousands of patients treated in clinical practice do not support oncologic equivalence of the two modalities, though this evidence is limited by selection bias. Complications following PCa treatment are relatively

common. These include the commonly identified issues of urinary incontinence and erectile dysfunction but also others including hospitalizations and invasive procedures to manage complications, and secondary malignancies (Table 3). Thus, well powered and designed randomized controlled trials continue to be needed in order to assess the true effectiveness of these treatments to provide the definitive answer enabling enhanced patient and clinician decision-making when active treatment of localized PCa is to be undertaken.

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AUTHOR CONTRIBUTIONS

Christopher J.D. Wallis had full access to all the data in the manuscript and takes responsibility for the integrity of the data and the accuracy of data presentation.

Study concept and design: Wallis, Glaser, Hu, Huland, Lawrentschuk, Moon, Murphy, Nguyen, Resnick, Nam

Acquisition of data: Wallis

Analysis and interpretation of data: Wallis, Glaser, Hu, Huland, Lawrentschuk, Moon, Murphy, Nguyen, Resnick, Nam

Drafting of the manuscript: Wallis

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Table 1. Key studies examining oncological outcomes of treatment of localized prostate cancer with radiotherapy and radical prostatectomy.

Study identifier	Design	Exposures	Sample size	Findings	Limitations
Hamdy et al.	Randomized controlled trial	Radical prostatectomy vs. EBRT + ADT	1098	No difference in PCSM (p=0.48) or OM (p=0.87)	-Underpowered -Over-representation of low risk patients
Lennernas et al.	Randomized controlled trial	Radical prostatectomy vs. EBRT + brachy boost + ADT	89	No difference in PCSM	-Underpowered
Wallis et al.	Meta-analysis of observational studies	Radical prostatectomy vs. radiotherapy (EBRT or brachy)	95,791	Increased OM and PCSM among patients treated with radiotherapy	-Residual confounding
Notes: EBRT = external beam radiotherapy; brachy = brachytherapy; ADT = androgen deprivation therapy; PCSM = prostate cancer specific mortality; OM = overall mortality.					

Table 2. Key studies examining functional outcomes of treatment of localized prostate cancer with radiotherapy and radical prostatectomy.

Study identifier		Hamdy et al.	Lennernas et al.	Gilberti et al.	Resnick et al.
Study design		Randomized controlled trial	Randomized controlled trial	Randomized controlled trial	Observational cohort study
Exposures		Radical prostatectomy vs. EBRT + ADT	Radical prostatectomy vs. EBRT + brachy boost + ADT	Radical prostatectomy vs. brachytherapy	Radical prostatectomy vs. EBRT
Sample size		1098	89	174	1655
Findings					
	Global HRQoL	Equivalent	Equivalent	Equivalent	-
	Incontinence	Greater in RP than RT	Equivalent	Equivalent	Greater in RP (at 2/5 yrs) Equivalent (at 15 yrs)
	Erectile dysfunction	Greater in RP than RT	Equivalent	Greater in RP (short-term) Equivalent (long-term)	Greater in RP (at 2/5 yrs) Equivalent (at 15 yrs)
	Bowel symptoms	Greater in RT than RP	Equivalent	Greater in RT (short-term) Equivalent (long-term)	Greater in RT (at 2/5 yrs) Equivalent (at 15 yrs)
	Obstructive urinary symptoms	Greater in RT than RP	Equivalent	Greater in RT (short-term) Equivalent (long-term)	

Notes: EBRT = external beam radiotherapy; brachy = brachytherapy; ADT = androgen deprivation therapy; RP = radical prostatectomy; RT = radiotherapy; yrs = years.

Table 3. A comparison of key outcomes following radical prostatectomy and radiotherapy in the treatment of localized prostate cancer, stratified by evidentiary study design.

Outcome	Randomized controlled trials		Observational cohort studies	
	Evidence	Caveats	Evidence	Caveats
Survival	No difference	Underpowered and over-representation of low-risk patients.	Significantly improved overall and prostate cancer-specific survival for patients treated with surgery	Residual confounding, with study design unable to fully account for baseline differences.
Global HRQoL	No difference	n/a	No difference	Residual confounding
Urinary function	Conflicting evidence: likely no long-term differences	n/a	Greater incontinence early after surgery and greater urinary bother after radiotherapy. No differences long-term.	Residual confounding
Erectile function	Conflicting evidence: likely no long-term differences	n/a	Worse erectile function early after surgery. No difference long-term.	Residual confounding
Bowel function	Worse after radiotherapy	n/a	Worse bowel function early after radiotherapy. No difference long-term.	Residual confounding
Other complications	No data		Increased risk of urologic and rectal-anal procedures, major surgeries, and hospitalizations to manage treatment-related effects after radiotherapy.	Residual confounding
Secondary malignancies	No data		Increased risk of bladder, rectal and colorectal cancer after radiotherapy.	Despite significant relative risk, small absolute risk. Residual confounding
Note: HRQoL = health-related quality of life.				