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

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38 **KEY WORDS:** prostatic neoplasms/mortality; radiotherapy/adverse effects;
39 prostatectomy/adverse effects; comparative effectiveness research; brachytherapy; quality of life

1 **ABSTRACT**

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

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

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

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

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

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

37

38

1 **1. INTRODUCTION**

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

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

1 **2. EVIDENCE ACQUISITION**

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

9

10 **3. EVIDENCE SYNTHESIS**

11

12 **3.1 Oncologic outcomes in prostate cancer research**

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

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

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

16

17 **3.1.1 Randomized survival data**

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

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

5 Two older randomized trials compared survival outcomes following radical
6 prostatectomy and radiotherapy. The first was conducted by the Uro-Oncology research group in
7 the pre-PSA era[16] and the second by the Japanese Study Group for Locally Advanced Prostate
8 Cancer more recently¹⁶. Both demonstrated improved outcomes in surgically treated patients,
9 however due to methodologic limitations (including insufficient follow-up) and the evolution of
10 medical practice (including stage migration due to the introduction of PSA screening), neither of
11 these studies have influenced current clinical practice.

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

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

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

8 **3.1.2 Observational survival data**

9 Considering the limitations among available randomized trials, a recent meta-analysis of
10 observational studies compared overall and prostate-cancer specific mortality for patients treated
11 with surgery and radiotherapy[22]. Utilizing pooled results of 95,791 patients for the outcome of
12 overall mortality and 118,830 patients for PCa-specific mortality, patients treated with
13 radiotherapy had a significantly increased risk of death (overall mortality: HR 1.63, 95% CI 1.54
14 – 1.73; PCa-specific mortality: HR 2.08, 95% CI 1.76 – 2.47). These findings were robust to
15 subgroup and sensitivity analyses including PCa risk categorization, study accrual period,
16 radiotherapy modality (EBRT or brachytherapy), duration of follow-up, and geographic region
17 of study[22]. It is notable that a survival benefit was found even among patients with low-risk
18 disease, likely reflecting a combination of the Will Rogers phenomenon[23] and residual
19 confounding.

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

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

10 There are many ways to account for selection biases, most principally confounding by
11 indication, in observational studies including regression techniques, propensity-score approaches
12 (including matching and weighting), and instrumental variable techniques. Many of the studies in
13 the meta-analysis included all identifiably relevant patient and tumor characteristics in regression
14 or propensity-score matched analyses[22]. While these approaches account for observed
15 confounders, instrumental variable analyses may also account for unmeasured confounding.
16 Using such an approach in patients with \geq ten-year predicted life expectancy, Sun et al. found
17 improved survival among those treated with surgery compared to radiotherapy (HR 0.66, 95% CI
18 0.56 – 0.79)[28]. While instrumental variable analyses have been shown to provide less biased
19 estimates of treatment effect[29], these techniques are unable to fully account for selection bias
20 and consequently residual confounding remains[30]. Furthermore, there remain important
21 statistical limitations with respect to their ability to determine differences in outcomes. To
22 address such residual confounding, Cooperberg et al. performed an elegant sensitivity analysis in
23 which Kattan scores were artificially increased for patients undergoing prostatectomy[31]. To

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

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

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

14

15 **3.2 Global health-related quality of life**

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

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

6

7 **3.3 Functional outcomes: “classic complications”**

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

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

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

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

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

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

3

4 **3.4 Functional outcomes: Novel complications**

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

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

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

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

7 In the Ontario cohort, patients treated with radiotherapy had a significantly increased risk
8 of secondary cancers (standardized incidence rate (SIR) 2.0, 95% CI 1.7-2.3), driven by an
9 excess of secondary cancers in men aged 40-65 at the time of radiotherapy (SIR 3.5, 95% CI 2.3-
10 4.7)[47]. This finding has recently been supported by a meta-analysis comprising 21 studies and
11 up to 555,873 patients[55] which found an increased risk of in-field secondary malignancies
12 (bladder, rectal and colorectal cancers) but not of out-of-field malignancies among patients
13 treated with radiotherapy, though the absolute risk was small (0-1.4 cases per 100 patients
14 treated)[55].

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

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

3

4 **3.5 Effect of Androgen Deprivation Therapy**

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

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

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

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

10

11 **3.6 Evolving treatment modalities**

12

13 **3.6.1 Changes in surgical approach**

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

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

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

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

12

13 **3.6.2 Changes in radiotherapy delivery**

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

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

7 In addition to the described advances in the delivery of EBRT, there has been significant
8 scientific interest in brachytherapy despite persistent and ongoing declines in its utilization[101-
9 103]. The recently reported ASCENDE-RT trial demonstrated that the addition of brachytherapy
10 boost to EBRT and ADT in men with intermediate- and high-risk disease was associated with
11 improved biochemical control and comparable overall survival[104]. Brachytherapy boost was
12 associated with increased genitourinary toxicity[105] and patient-reported worse overall health,
13 sexual function, and urinary function[106].

14

15

16

17 **4. CONCLUSIONS**

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

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

7

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11

12 **AUTHOR CONTRIBUTIONS**

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

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

17 **Acquisition of data:** Wallis

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

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22 Lawrentschuk, Moon, Murphy, Nguyen, Resnick, Nam

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26 **Supervision:** Nam

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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.

