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Late Genitourinary Toxicity Following External Beam Radiotherapy for Prostate Cancer

By

Rowan Victor David
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MPH

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Publications Related To This Thesis

Incidence and Burden of Treatment of Genitourinary Complications following Radiation Therapy for Localised Prostate Cancer.

World Journal Urology 2022.

Rowan David, Arman Kahokehr, Jason Lee, John Leung, David Watson, Michael O'Callaghan.

Predicting genitourinary toxicity after radiotherapy treatment for localised prostate cancer

World Journal Urology 2022.

Rowan David, Mrunal Hiwase, Arman Kahokehr, Jason Lee, John Leung, David Watson, Michael O'Callaghan.

Long Term Genitourinary Toxicity Following Curative Intent Intensity-Modulated Radiotherapy For Prostate Cancer: A Systematic Review and Meta-analysis.

Prostate Cancer and Prostatic Diseases March 2022.

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Genitourinary Toxicity After Pelvic Radiation: Urological Presentations To A Tertiary Unit

Asian Journal of Urology 2023.

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Publications Unrelated To This Thesis During Candidature

Penile Gangrene Due To Calciphylaxis - A Multidisciplinary Approach To A Complex Clinical Challenge.

BMJ Case Reports 2019.

Rowan David, Nicola Dean, Jason Lee.

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Surgical Locker-room Environment: Understanding the Hazards (SLEUTH) Study.

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A Prospective Case Series of Fournier's Gangrene at a Tertiary Centre Involving Adjacent Organs.

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Michael O'Callaghan, David Watson, Jason Lee

Burden Of Treatment And Cost Associated With Haemorrhagic Radiation Cystitis In Patients With Prostate Cancer.

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Long Term Genitourinary Toxicity Following Curative Intent Intensity-Modulated Radiotherapy For Prostate Cancer: A Systematic Review and Meta-analysis.

Moderated Poster Presentation British Association of Urological Surgeons 2020.

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Genitourinary Toxicity After Pelvic Radiation: Prospective Review of Complex Urological Presentations.

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Predicting Genitourinary Toxicity After Radiotherapy Treatment for Localised Prostate Cancer.

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Comparison of Patient-Reported Outcomes Measures in Patients with Localised Prostate Cancer Following External Beam Radiotherapy or Radical Prostatectomy.

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Enlarging Giant Pelvic Desmoid Tumour: A Multidisciplinary Approach

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Adequacy of Retrograde Urethrogram in Surgical Decision Making for Anterior Urethral Stricture Disease: A Prospective Study.

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Surgical Locker-room Environment: Understanding the Hazards (SLEUTH) Study

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A Prospective Case Series of Fournier's Gangrene at a Tertiary centre Involving Adjacent Organs.

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Rowan David, Luke Traeger, Sean Chang, Penelope Cohen, Arman Kahokehr, Akbar Ashrafi.

Early Activation of Artificial Urinary Sphincter for PPSUI is safe: A Pilot Study.

Oral presentation at ICS 2021.

Rowan David, Thomas Cundy, Arman Kahokehr.

Ureteral Stenting for Malignant Ureteral Obstruction: A Prospective Study

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Rowan David, Alex Buckby, Arman Kahokehr.

Thesis Summary

Background. Prostate cancer is common and often treated with radiation therapy. Some patients present to urology centres with treatment-related genitourinary (GU) toxicity following external beam radiotherapy (EBRT). However, the incidence and predictors of late GU toxicity occurring more than five years after EBRT remains under-reported.

Purpose. This thesis aims to examine GU toxicity following EBRT for localised prostate cancer. Firstly, we describe the incidence of GU toxicity reported in randomised controlled trials. Secondly, we determine the treatment burden associated with GU toxicity at a single institution. Thirdly, we determine the 10-year cumulative incidence of treatment-related GU toxicity at a population level. Finally, we develop, assess, and validate a novel model to predict GU toxicity for pre-treatment counselling.

Methods. Firstly, articles published from January 2008 - December 2021 describing prospective studies were systematically searched in MEDLINE and EMBASE. Meta-analysis was performed on the 60-month incidence of late genitourinary toxicity. Next, a prospective study was performed of all patients who presented to a tertiary urology department over 12 months with GU toxicity after pelvic radiotherapy. Subgroup analysis was performed on patients with prostate cancer. Thirdly, a prospective population-based cohort, including hospital admission and cancer registry data, for men with localised prostate cancer who underwent primary EBRT without nodal irradiation between 1998 and 2019 in South Australia was analysed to determine the cumulative incidence of treatment-related GU Toxicity. Finally,

a multivariable Cox proportional hazards model was developed to predict GU toxicity following EBRT. Model discrimination, calibration, internal validation, and utility were assessed using C-statistics, calibration plots, bootstrapping, and decision curve analysis.

Results. The systematic review included six studies (n=4,634), and meta-analysis revealed pooled 60-month cumulative incidence of (Radiation Therapy Oncology Group) RTOG and (Common Terminology Criteria for Adverse Event) CTCAE Grade ≥2 genitourinary toxicities of 17% (95% CI: 5-28%, n=678) and 33% (95% CI: 27-38%, n=153), respectively. Next, the prospective single-institution study (n=46, 117 admissions) determined that GU toxicity accounted for 3% of 1,524 urological admissions over 12 months. Patients with prostate cancer were associated with higher median RTOG scores (p=0.037), emergency admissions (p=0.048) and clot urinary retention (p<0.001). Following this, the population cohort study (n= 3,350) revealed a 10-year cumulative incidence of hospital admission and urological operative procedure of 28.4% (95% CI 26.3 – 30.6) and 18% (95% CI 16.1 – 19.9), respectively. Furthermore, diabetes (HR 1.28, 95% CI 1.08-1.53, p = 0.004), smoking (HR 1.67, 95% CI 1.40 – 2.00, p < 0.001), and bladder outlet obstruction without transurethral resection of prostate (HR 5.87, 95% CI 4.80 – 7.17, p < 0.001) were strong predictors of hospitalisation in multivariable analysis and the model performed well (censor-adjusted c-statistic = 0.80, AUC 0.75).

Conclusion. GU toxicity after EBRT for prostate cancer is common. Based on the meta-analysis and population-level data, the conservative estimated rates of GU toxicity are high. This is the first study to develop a predictive model for GU toxicity requiring hospitalisation amongst men with prostate cancer treated with EBRT.

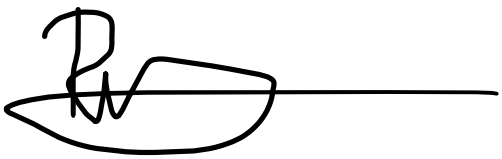
Declaration

I certify that this thesis:

1. does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university

2. and the research within will not be submitted for any other future degree or diploma without the permission of Flinders University; and

3. to the best of my knowledge and belief, does not contain any material previously published or written by another person except where due reference is made in the text.



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Abbreviations

3DCRT: Three-dimension conformal radiation therapy

ADT: Androgen Deprivation Therapy

BOO. Bladder Outlet Obstruction.

CTCAE: Common Terminology Criteria for Adverse Events.

GI: Gastrointestinal.

GU: Genitourinary.

GUT: Genitourinary Toxicity.

Gy: Gray.

IMRT: Intensity-modulated radiotherapy.

NCCN: National Comprehensive Cancer Network.

PPD: (Urinary Continence) Pads Per Day

PSA: Prostate-Specific Antigen.

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

PROMS: Patient-Reported Outcome Measures.

QUIPS: Quality in Prognosis Studies.

RTOG: Radiation Therapy Oncology Group.

TURP: Transurethral Resection of Prostate.

TURBT: Transurethral Resection of Bladder Tumour

TRO: Treatment-Related Outcome.

UI: Urinary incontinence.

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Chapter 1: Introduction

Background

Prostate Anatomy and Physiology

The prostate is a dense fibromuscular gland that approximates the shape of an inverted cone. The prostate gland is located inferior to the urinary bladder within the male pelvis. Notably, the prostate gland encircles the proximal urethra. The two ejaculatory ducts enter the prostate shortly after emerging from the abutting seminal vesicles. These ejaculatory ducts travel from posterolateral to inferomedial relative to the prostate and converge within the prostatic urethra at the seminal colliculus. The prostate is enclosed by a fibrous capsule and a further visceral layer of pelvic fascia. The nerves and vascular structures that supply the prostate and adjacent structures pass between these layers.

Walsh, in 1982 highlighted the association between intraoperative nerve damage and iatrogenic impotence in patients undergoing radical prostatectomy. (1) However, the relationship of the neurovascular bundle relative to the prostate has been controversial in the literature. The neurovascular bundle was initially described as travelling posterolateral to the prostate between its course from the pelvic plexus to the corpora cavernosa. (1) Several publications have indicated that the path of the neurovascular bundle tends to be more variable than originally described, especially anteriorly to the prostate. (2-6) Recently, the path of the neurovascular bundle was re-analysed by Clarenborough et al. using novel cross-sectional imaging analysis of 13 cadaveric models. (7) Clarenborough et al. determined a significantly larger cross-sectional volume of neural tissue travelling

along the posterior relative to the anterior surface of the prostate. (7). Furthermore, there were increased proportions of periprostatic neural tissue cross-sectional area from the apex towards the base of the prostate, with 11.2%, 7.6% and 6% of tissue on the anterior surface of the base, mid and apical regions of the prostate, respectively. (7). Several other studies also support this finding of increased total periprostatic neural bundles at the apex relative to the prostate base. (6, 8)

The prostate has several close relations to nearby vital structures. Anterior to the prostate is the pubic symphysis and prostatic venous plexus, which are separated by the retropubic fat pad. Posterior to the prostate is the rectum, which is separated only by Denonvillier's fascia. Inferior to the prostate is the external urethral sphincter, which encircles the urethra to control urinary flow and ejaculation. Lateral to the prostate gland are the Levator ani muscles of the pelvic floor, which are covered by the endopelvic fascia. (9)

The prostate gland forms part of the male reproductive system. The primary purpose of the prostate gland is to secrete alkaline fluid to protect sperm from the acidic vaginal fluid. In addition, prostatic fluid also contains proteins and enzymes that nourish the spermatocytes. The prostatic fluid also increases the volume of the seminal fluid to allow for improved mechanical propulsion of sperm through the urethra. (9)

Prevalence & Incidence

Prostate cancer is the second most common cancer affecting men worldwide and has become the most common malignancy amongst men in Australia and Europe. (10, 11) The rising prevalence of prostate cancer is partly due to population ageing. (12) A growing proportion of younger men are also diagnosed with prostate cancer. (13) There have been remarkably rapid increases in the incidence of prostate cancer in Western countries, partly because of the widespread increase in opportunistic screening for prostate cancer using prostate-specific antigen testing. (13-15)

Population screening with PSA testing has led to the detection of some patients with early-stage prostate cancer that will not cause significant symptoms during their lifetime. (16) The majority (94%) of patients with prostate cancer have curable localised disease with a good prognosis, and survival is increasing. (17) The high five-year prostate-cancer-specific survival rates (98.8%) following curative intent treatment for localised disease leave a large cohort of men at risk of developing adverse effects from their cancer treatment (both short- and long-term). (18-23) Quality of life is a crucial concern amongst patients with localised prostate cancer who are considering treatment options, given the excellent oncological control rates with treatment. (24) More research is required to avoid or minimise treatment-related toxicity amongst men with prostate cancer who undergo curative intent treatment.

Prostate Cancer Screening

A screening test in this context of the male population can be defined as the 'systematic examination of asymptomatic men to identify individuals at risk'. (25) Ultimately, screening aims to improve disease outcomes within a particular population. Screening can also be individualised on the patient's request and referred to as 'opportunistic screening' or 'early detection'.(26) Prostate cancer screening typically involves a PSA test and a digital rectal examination.

Prostate-specific antigen (PSA) is a glycoprotein customarily released by prostate tissue. (27) Currently, the European Association of Urology guidelines by Van Poppel et al. in 2021 recommend a risk-adapted strategy for the early detection of prostate cancer. (28) However, the recommendations on whether PSA surveillance should be performed have been long debated in the literature. (29)

Before PSA testing was introduced in the late 1980s, of every three men diagnosed with prostate cancer, one to two would die from the disease. (30) Hence, PSA testing was initially introduced as population-level mass screening and led to a reduction in prostate cancer-specific mortality rates. (31) (32) The study by Catalona et al. in 1991 reported that PSA-driven biopsy was associated with significant downstaging of prostate cancer at the initial diagnosis. (33)

However, there was a lack of understanding regarding the specificity of PSA and the natural history of prostate cancer. Firstly, whilst PSA is specific to the prostate, it is not cancer-specific and is often elevated in other benign prostate conditions, including benign prostatic hyperplasia and prostatitis. (25) Secondly, there was no appreciation of the difference between clinically significant and insignificant prostate cancer. Many men with PSA screening-detected prostate cancer harbour disease that may be indolent during their lifetime. (34) Thirdly, there are issues regarding the sensitivity of PSA in prostate cancer diagnosis. (25) The prostate cancer prevention trial (PCPT) followed approximately

5000 men aged at least 55 years with an initial PSA < 3.0 ng/ml over seven years. The trigger for prostate biopsy in this study was a PSA rise to >4.0 ng/ml with or without an abnormal rectal examination, which resulted in a prostate cancer diagnosis rate of 21.9%. However, using a cut-off value of 3.0 ng/ml for prostate biopsy, 64% of patients with detectable cancers and 42% of potentially aggressive cancers would be missed. (35) Therefore, using any cut-off value for PSA testing will ineluctably miss patients with prostate cancer and a lower percentage of men with more aggressive disease. Finally, there is no international standard defined for PSA measurement. (36) Due to these fundamental misconceptions, patients with prostate cancer were often overtreated with local curative intent radical treatments, which left them at risk of developing a range of treatment-related adverse events.

The trend away from PSA surveillance is highlighted by the changes in policy promoted by the United States Preventative Services Task Force (USPSTF). In 2002, the USPSTF recommended PSA testing to detect early prostate cancer despite acknowledging the paucity of evidence regarding its impact on health outcomes. (37 909) In 2008, the USPSTF added the recommendation that men over 75 should not be screened for prostate cancer. (38) In 2012, the USPFT reversed their position for PSA-based screening entirely and recommended against PSA-based screening for all men without a prior prostate cancer diagnosis. (39) Currently, the USPFT recommends against PSA screening in younger men (40-55 years) and those over 70. The decision to undergo PSA testing amongst men between these ages should be made individually during a discussion with their clinician regarding the potential benefits and harms. (40) This change resulted from the significant decline in PSA testing due to the prior recommendations, which led to a decrease in the diagnosis of localised prostate cancer and a rise in the diagnosis of locally advanced and metastatic disease, as reported in 2017. (41-43) Furthermore, there was a concerning plateau in the rates of prostate cancer-specific mortality, which had previously been on a downwards trend over the past two decades. (31)

Since then, two large RCTs have been performed evaluating PSA screening, including the European Randomised study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colorectal and Ovarian (PLCO) Screening trials. (44, 45) The ERSPC trial evaluated 182,160 men and determined that PSA screening significantly reduced the rate of prostate cancer-specific mortality by 20% at 16 years of follow-up (RR 0.80, 95% CI 0.72–0.89). (44) The PLCO Cancer Screening trial did not demonstrate an association between PSA screening and a reduction in prostate cancer-specific mortality. (45) However, a recent age and trial-adjusted modelling analysis demonstrated compatible evidence that PSA screening reduces prostate cancer-specific mortality amongst both the ERSPC and PLCO trials. (46)

Recently, the Urological Society of Australia and New Zealand (USANZ) endorsed the Prostate Cancer Foundation of Australia (PCFA) recommendations on PSA- testing. (47) These guidelines support clinician counselling before PSA testing for men between 50 and 69, including an evidence-based discussion of the benefits and harms of testing. For informed men at average risk of prostate cancer, who wish to pursue PSA testing, alternate yearly PSA testing is recommended with a threshold of > 3.0 ng/mL set for further investigation. However, criteria proposed by the PCFA are much broader than other guidelines, such as the EAU.

Prostate Cancer Diagnosis

A prostate tissue core biopsy is required to diagnose prostate cancer. (25, 27) Histopathological examination of the tissue samples also determines the grade of prostate cancer. The most predominant (primary) and subsequent most common (secondary) patterns are determined. The global Gleason grade is calculated based on the combined primary and secondary grades as well as the extent of each grade from all the sampled prostate tissue. If only one pattern is present, it is doubled to determine the overall Gleason grade. (48) The latest 2014 International Society of Urological Pathology (ISUP) grading system then scores the prostate cancer grades from one to five. (48, 49)

Patients with prostate cancer have been categorised into those with 'clinically significant' and 'clinically insignificant' diseases. Prostate cancer considered 'clinically significant' may result in prostate-cancer-specific morbidity or mortality during the patient's expected lifetime. Prostate cancer that is 'clinically insignificant' reflects a disease that does not lead to harm for the patient. The distinction is imperative following the diagnosis of prostate cancer because 'clinically insignificant' prostate cancer is commonly diagnosed and may be overtreated. (50) The over-treatment of patients with 'clinically insignificant' prostate cancer is a significant limitation of PSA testing. These patients are at risk of treatment-related adverse events and a poor therapeutic ratio. (39) However, there is a lack of consensus regarding the definition of clinically significant prostate cancer. (25) Recent papers have extended the definition of clinically insignificant prostate cancer to include even ISUP 3 disease. (51-54)

Defining Localised Disease

Clinicians typically categorise prostate cancer into three main stages, according to the Tumour, Node, Metastasis (TNM) classification for the staging of prostate cancer. (55) Localised prostate cancer refers to patients with T1, T2 or early T1 disease in the absence of nodal (N0) or metastatic (M0) disease. Locally advanced prostate cancer refers to patients with established T3 or T4 disease with or without nodal metastasis (N0/N1) but without any distant metastatic disease (M0). (56, 57) Lastly, there are patients with prostate cancer who have metastatic disease (M1). This thesis focuses on men with non-metastatic prostate cancer, including localised and locally advanced disease.

Most (94%) patients with prostate cancer have curable localised disease. (17) Patients with localised prostate cancer are usually asymptomatic at the time of diagnosis. While patients may report lower urinary tract symptoms at the time of diagnosis, this is usually due to concurrent benign prostatic hyperplasia (BPH). More than 50% of men over 50 will develop lower urinary tract symptoms because of BPH. Less commonly, men diagnosed with prostate cancer may also develop lower urinary symptoms from concurrent urinary tract infection, urethral stricture, and overactive bladder syndrome. Hence, patients with lower urinary tract symptoms, due to other causes, are often incidentally diagnosed with non-aggressive prostate cancer, with a limited or negligible impact on their overall survival. In rare cases, prostate cancer can present as new-onset erectile dysfunction, haematuria, or haematospermia. (58)

Treatment Options

Patients with prostate cancer are only considered candidates to benefit from active treatment if they have a life expectancy of at least ten years.(25) Numerous studies have consistently reported a cancer-specific survival rate ranging from 82% to 87% at 10 years amongst men with newly diagnosed prostate cancer. (59-64) Age and comorbidity are essential factors in estimating the life expectancy of men with prostate cancer. Albertsen et al highlighted the importance of evaluating a patient's comorbidity prior to considering a prostate biopsy. Albertsen et al. demonstrated in an age-adjusted analysis of 19,639 men aged over 65 years with prostate cancer who did not receive curative treatment that most men with a Charlson comorbidity score $\geq$ 2 died from competing causes after 10 years of follow-up. Prostate cancer grade had minimal impact on patient overall survival, suggesting that prostate biopsy may not be necessary for these patients. (65) Prostate cancer-specific mortality amongst patients with untreated ISUP grade 1-2 prostate cancer, which was detected via screening, may be as low as 7% at 15 years of follow-up. (66)

The active treatment options for localised prostate cancer include active surveillance or curative treatments, such as radical prostatectomy or radiotherapy. Currently, there is limited evidence to suggest that either radical prostatectomy or radiotherapy for localised prostate cancer has superior oncological outcomes. (67-71) Therefore, patients with prostate cancer are faced with a unique situation whereby they are provided with a choice of more than one treatment option with similar efficacy.

Active Surveillance

Active Surveillance (AS) incorporates a structured monitoring strategy for men with clinically localised prostate cancer. Active Surveillance aims to potentially avoid unnecessary curative treatment, which is frequently associated with side effects.(72) Active Surveillance also aims to select patients more discriminately for curative treatment who may eventually require treatment. (73) Active Surveillance involves close monitoring of patients with prostate cancer via regular outpatient follow-up appointments to review digital rectal examination findings, prostate-specific antigen levels, magnetic resonance imaging, and repeat prostate biopsies. The need for curative treatment is prompted by pre-defined thresholds suggestive of potentially aggressive but curable disease. (25)

Active Surveillance has been proven to be a safe option amongst patients with favourable-risk disease. (74, 75) An increasing number of men worldwide are opting for active surveillance. (76) However, no formal RCT is available comparing Active Surveillance to radical prostatectomy or radiotherapy. The ProtecT trial is discussed in the comparative chapters of this thesis but involves much less stringent active monitoring rather than a formal Active Surveillance strategy. (77)

Radical Prostatectomy

Radical prostatectomy (RP) is another option recommended for men with over ten-year life expectancy and intermediate or high-risk localised prostate cancer who are fit for surgery. RP aims to surgically remove the entire prostate with an intact capsule and seminal vesicles while preserving pelvic organ function. (78) A nerve-sparing approach can be taken during RP, which leaves the neurovascular bundles intact to preserve erectile function. (79, 80) If patients are correctly selected for a nerve-sparing approach, there should be no compromise in their oncological outcome. (81-83)

There has been an evolution in surgical techniques, with the open retropubic prostatectomy almost entirely replaced with less invasive laparoscopic or robot-assisted prostatectomy (RALP). (84) The open retropubic approach was presented by Walsh et al. in 1982 and helped to facilitate bilateral nerve-sparing.(1) More recently, RALP was reported by Binder et al. in 2002 using the da Vinci Surgical System.(85) The introduction of RALP improved surgeon ergonomics and technical ease of suturing and has since become the preferred minimally-invasive approach.(25) While minimally invasive surgery has known advantages, randomised control trials have yet to demonstrate significant improvement in post-operative oncological or functional outcomes over open surgery amongst men with prostate cancer. (86)

Patient outcomes following RP depend on surgeon (87) and hospital volume. (88) However, there is currently an insufficient level of evidence available to define a specific lower volume limit.(25) Functional urological complications, including urinary incontinence and erectile dysfunction, are common amongst patients with prostate cancer who undergo RP.(25)

Radiotherapy +/- Androgen Deprivation Therapy

Radiotherapy is a commonly utilised treatment for localised prostate cancer. (89-93) External beam radiation therapy or brachytherapy can deliver radiation therapy to the prostate. Radiotherapy is often given in combination with neoadjuvant or adjuvant hormonal therapy. (25) Radiation treatment regimens for patients with prostate cancer are limited by the risk of radiation-induced toxicity to normal structures. However, the possibility of radiation-induced toxicity is balanced against the likelihood of underdosing target areas, which could impair local treatment outcomes. (94) Despite changes in radiation planning and delivery methods that aim to improve the therapeutic ratio of cancer control, some patients may still suffer long-term genitourinary sequela. (95, 96)

There is robust evidence supporting the use of combined radiotherapy and ADT for men with intermediate or high-risk localised prostate cancer to optimise treatment efficacy. (97) (98) The recent meta-analysis by Zapatero et al. involving 12 randomised trials using individual patient data of men with prostate cancer receiving definitive radiotherapy (n= 10,853) determined that ADT use was associated with significant improvements in biochemical recurrence, metastatic recurrence, metastasis-free surgical and overall survival over 11 years median follow-up. ADT was an independent predictor of improved outcomes when controlled for radiotherapy dose, age and NCCN disease risk. (98) Three RCTs have shown that the benefits of ADT are independent of dose escalation and that the use of ADT would not compensate for a lower RT dose. (98, 99, 100 The GIGOR RCT demonstrated improved biochemical disease free surgical in patients with high-risk prostate cancer treacted with 3D-CRT (dose > 72Gy) when combined with long-term ADT. {Zapatero, 2005 #8917) The DART01/05 GICOR RCT demonstrated improved ten-year overall survival associated with high-dose RT and two years of adjuvant ADT use than high-dose RT alone in men with high-risk prostate cancer. (100) The EORTC trial 22991 demonstrated that in men with intermediate-risk and low-volume high-risk

localised prostate cancer, six months of ADT use was associated with improved biochemical and disease-free surgical independent of RT dose (70, 74, 78 Gy). (99) The strong evidence supporting concurrent EBRT and ADT use suggest that this practice will continue. Patients will then continue to be exposed to the additional toxicity associated with concurrent EBRT and ADT use.

Focal Therapy

Focal therapy for men with prostate cancer is an umbrella term for a range of minimally invasive techniques used to treat lesions within the prostate whilst sparing the normal surrounding prostatic tissue. These ablative techniques include various methods, including high-intensity focused ultrasound, laser and cryotherapy. Focal therapy aims to spare men with localised prostate cancer the potential treatment-related adverse effects of standard whole gland therapy whilst maintaining equivalent oncological outcomes. (101) However, there is currently a lack of randomised data and long-term outcomes supporting the role of focal therapy for men with prostate cancer. (101)

Current guidelines recommend that focal therapy only be used for prostate cancer treatment in an investigative setting. (101-103)

The EAU Guidelines include the following recommendations for men with newly diagnosis prostate cancer:

- "Only offer FT within a clinical trial setting or well-designed prospective cohort study (for low- and intermediate-risk disease (Strong))"
- "Do not offer either whole-gland therapy or FT to patients with high-risk localised disease (Strong)"

Whilst the AUA Guidelines include the following recommendations for men with newly diagnosis prostate cancer: (103)

- "Clinicians should inform patients WITH low-risk PCa who are considering FT or HIFU that these interventions are not standard of care options because comparative outcome evidence is lacking. (Expert Opinion)"

- "Clinicians should inform patients with intermediate-risk prostate cancer considering whole gland or focal ablation that there are a lack of high-quality data comparing ablation outcomes to radiation therapy, surgery, and active surveillance. (Expert Opinion)"
- "Cryosurgery, FT and HIFU treatments are not recommended for men with high-risk localised PCa outside of a clinical trial. (Expert Opinion)"
- "As PCa is often multifocal, clinicians should inform patients with localised PCa considering FT that FT may not be curative and that further treatment for PCa may be necessary. (Expert Opinion)"

The National Comprehensive Cancer Network Guidelines state that: (101)

- "Cryotherapy or other local therapies are not recommended as routine primary therapy for localised PCa due to lack of long-term data comparing these treatments to RT or RP."

The Urological Society of Australia and New Zealand have recently promoted a prospective study of men with clinically localised prostate cancer treated with focal therapy involving a novel laser device for men, which reports no treatment-related toxicity in interim 3-month follow-up results. (104)

Theranostic

Radiopharmaceutical therapy is predicted to have an increasing role of the management of men with prostate cancer. Radiopharmaceutical therapy involves the delivery of radioactive atoms to tumour-associated targets, leading to radiation-induced cell death. The radionucleotide ^{177}Lu is commonly favoured as a theranostic agent because of its ideal imaging range (100–200 keV), favourable half time (6.6 days) and appropriate β-particle energy for therapy. Additionally the short path of the α-particle (0.05–0.08 mm) has been thought to minimise adjacent normal tissue toxicity. (105) ^{177}Lu has recently been approved by the Food and Drug Administration for the treatment of adult patients with Prostate Specific Membrane Antigen-positive metastatic Castrate Resistant Prostate Cancer who have been treated with Androgen Receptor Pathway Inhibitors and taxane-based chemotherapy (106)

Changes in Radiotherapy Delivery

Three-dimension conformal radiation therapy (3DCRT) was developed to deliver an increased radiation dose conforming to the volume of the tumour target with significantly reduced exposure to healthy tissue. (89, 107-111) An advanced form of 3DCRT, known as Intensity-modulated radiotherapy (IMRT), evolved to generate a non-uniform field to increase the radiation dose delivered to the intended target. Intensity modulation with image-guided radiation therapy (IGRT) aims to improve the therapeutic ratio by minimising the dose to normal tissues, decreasing toxicity, and improving quality of life. (112)

There has been increasing use of image guidance in the delivery of IMRT, which has led to improved RT precision and sparing of radiosensitive normal tissues, including the bladder, enabling considerably higher doses of RT. (24, 113) Despite these technological improvements in prostate EBRT delivery, there has not been a consistent reduction in treatment-related late genitourinary (GU) toxicity demonstrated over the last decade. (114-116)

Changes in Radiotherapy Dose

Dose escalation with hypofractionation aims to exploit the radiobiology of prostate cancer to improve the therapeutic radio between disease-specific survival and quality of life of patients with prostate cancer undergoing radiotherapy. (24) Dose escalation was introduced because of its advantages in improving biochemical progression-free survival. (110, 117-123) However, dose-escalated radiotherapy has not demonstrated improved overall survival in men with prostate cancer.(108, 110, 119, 120) Furthermore, dose escalation has been associated with increased normal tissue toxicity, including late genitourinary toxicity.(108, 117, 124-128)

The literature review by Budaus et al. of the published literature (1999-2010) on GU and GI functional outcomes concluded that there might be less dose sparing associated with urinary (urethra and bladder neck) relative to rectal sparing during dose-escalated image-guided radiotherapy.(128) The study by Zelefsky et al. of men (n= 1571) with localised (T1-T3) prostate cancer treated with either 3D-CRT or IMRT between 1988-2000 reported that high-dose IMRT (81Gy) was associated with a significantly higher 10-year incidence of grade ≥2 GU toxicity (20% vs. 12%, p=0.01) than lower-doses. (127) The risk of developing secondary malignancy after radiotherapy may be increased with IMRT compared to conventional radiotherapy because of the increased total body exposure to radiation. (129-132) Despite these limitations, radiation oncologists adopted dose escalation globally.(107, 133, 134)

Genitourinary Toxicity

Each treatment for patients with localised prostate cancer is associated with a different side effect profile and the subsequent impact on the patient's health-related quality of life. (135-137) Radiotherapy injuries can remain asymptomatic for a long time (≥five years), and the difficulty in accurately recording these long-term adverse effects is frequently reported in the literature. (138, 139) Gardner et al. highlighted that late toxicity may be underestimated by an inadequate duration of follow-up and reported a 59% 15-year incidence of grade ≥ 2 genitourinary toxicity after 77.4 Gy 3D-CRT in patients with prostate cancer. (139) Attempts to determine the radiotherapy-related genitourinary toxicity rate are complicated by the numerous different toxicity grading systems. (19, 140-147) The Radiation Therapy Oncology Group (RTOG) is one of the dominant scoring systems reported in the oncology literature. However, the RTOG grading system has undergone numerous iterations to improve its accuracy. Whilst the Common Terminology Criteria for Adverse Events (CTCAE) is promoted as the comprehensive standard for reporting treatment-related adverse events in oncological care, it is often underutilised in trials. Hence the incidence of late genitourinary toxicity following prostate radiotherapy remains poorly characterised. (148-150)

Patients with prostate cancer who undergo EBRT risk developing a range of treatment-related genitourinary sequelae. These treatment-related complications include haemorrhagic cystitis, ureteric and urethral strictures, necrotic bladder neck, urinary fistula, urinary incontinence, retention, and erectile dysfunction. (151-158)

The true incidence of haemorrhagic radiation-induced cystitis has been controversial, with reported estimates ranging from 2.6% to 12.1%. (159-161) Patients who develop radiation-induced urethral

strictures and bladder neck contractures can be affected by bothersome obstructive voiding symptoms that can negatively impact their quality of life.

Similarly, patients can also develop lower urinary tract symptoms. These treatment-related lower urinary tract symptoms are typically due to bladder overactivity, which occurs more commonly following EBRT than RP. (162) Stress urinary incontinence can also occur, and the risk is higher after RP than EBRT. (162)

Sexual dysfunction remains the most common complication amongst prostate cancer survivors and significantly contributes to the health-related quality of life burden in cancer survivorship. (163) Erectile dysfunction is a well-recognised and challenging adverse effect after prostate radiation treatment, with rates varying from 6 to 84% following external beam radiotherapy and from 0 to 51% after brachytherapy. (154-158, 164, 165) Erectile dysfunction is defined broadly as the inability to get an erection, maintain an erection, or erections not satisfactory for sexual intercourse. The erectile nerves pass alongside the prostate and can be injured with radiation therapy. There have been five systematic reviews investigating erectile dysfunction outcomes following prostate radiation therapy.(154-158) The systematic review by Gaither et al. included 105 articles involving 26,269 men with known baseline erectile function prior to radiation therapy. In this cohort, 65% were treated with brachytherapy, 31% with external beam radiotherapy, and 4% with both treatments. Gaither et al. found erectile dysfunction prevalent in approximately 50% of patients at five years, as per Sexual Health Inventory for Men (SHIM). Pooled estimates of erectile dysfunction based on SHIM (score <10-17) suggested a 34% (95% CI = 0.29-0.39) prevalence rate of erectile dysfunction after radiotherapy at one year and 57% (95% CI = 0.53-0.61) at 5.5 years. (158)

The systematic review by Baker et al.(154) included 24 articles reporting functional quality of life outcomes following treatment for localised prostate cancer. Baker et al.found that sexual dysfunction was a more common adverse event in the men treated with radical prostatectomy than with radiotherapy. The review highlighted key findings in two articles, that reported the amplifying effect associated with concurrent ADT use amongst men with localised prostate cancer treated with EBRT. (166, 167) Sanda et al., 2008 reported that men who undergo EBRT for localised prostate cancer develop considerably worse sexual dysfunction in the setting of older age, larger prostate, higher pretreatment PSA level and adjuvant ADT use. (166) Furthermore, Chapple & Ziebland, 2002 report that men's perception of their masculinity is often threatened following treatment for localised prostate cancer, and that this effect is heightened by the adjuvant ADT use. (167)

However, many of the included studies had several significant limitations, including a lack of reporting of baseline sexual function data, variation in data collection time points, and poor generalisability of findings from treatments received over two decades ago. Unfortunately, a meta-analysis could not be performed due to variations in patient age range and timing of data collection. The relatively more decline in sexual function observed in surgery patients compared to radiation patients was also supported by Lee et al. in their systematic review of post-treatment EPIC scores across 26 articles published before 2012, involving 8302 patients.(155)

The systematic review by Bernard et al. included 13 studies from a search of Pubmed Central, CINAHL, SCOPUS, and EMBASE before June 2014 involving the effect of radiotherapy on the structure and function of pelvic floor muscles.(157) One of the included studies presented strong evidence that radiotherapy affects pelvic floor muscle structure in men treated for prostate cancer. However, meta-analysis was not possible due to heterogeneity and lack of descriptive statistics.

However, other studies suggest that the incidence of erectile dysfunction is likely over-reported in the post-radiotherapy setting. (168) Buckstein et al. analysed a cohort of patients (n=2046) who

underwent definitive radiotherapy (BT +/- EBRT) with a 6-year median follow-up (range 2-17 years). The incidence rate per 1000 patients for 0-2 years, 2-5 years, and 5-10 years after radiotherapy for erectile dysfunction was 82.4, 48.2, and 42.2, respectively. However, the study found that age was the only independent predictor of time to the onset of erectile dysfunction in multivariable analysis, suggesting that radiation-induced erectile dysfunction may be over-reported. (168)

Radiation-associated secondary malignancy (RASM) is well described in the literature after curative intent radiotherapy for prostate cancer. However, the incidence and clinical significance of radiation-associated secondary malignancy following pelvic radiation remain controversial. (169-171)

What Does The Evidence Say Regarding Treatment Selection?

There is no evidence-based consensus for men with early prostate cancer in deciding between active treatment or active surveillance regarding whether the benefits outweigh the harms of treatment-related adverse events. International guidelines, such as the EAU (172) and the AUA (173), base recommendations for treatment options on the classification of disease risk instead of patient-specific treatment-related toxicity risk. The professional opinions of Urologists and Radiation Oncologists regarding the best treatment option may be biased in favour of their respective specialty. These differences in opinions can obfuscate the treatment selection process for patients. (15, 174) Ultimately, the best treatment in terms of long-term survival remains unknown. (15). However, it is known that the adverse effects associated with each treatment can negatively affect patient well-being and quality of life. (175-179)

Recent studies have suggested that clinical pre-treatment metrics are essential factors determining the success of radiotherapy treatment regimens. (94) However, predictive models classically have been limited to mechanistic analysis of dose-volume metrics, including Lyman-Kutcher-Burman (180), dose-volume histogram (i.e., total bladder dose) (181, 182), and Area under the Histogram Curve (i.e., bladder wall contouring) (182) models, which are often already incorporated into radiotherapy delivery planning systems. Identifying pre-treatment clinical risk factors for the development of treatment-related toxicity is required to reduce the incidence and severity of radiotherapy-related genitourinary toxicity. (128, 183)

Patient-Centred Care in Decision Making

Patient decision-making regarding intervention options is often based upon physician discussion regarding oncological outcomes and adverse events. (166) The importance of patients with localised prostate cancer understanding these side effects before undergoing treatment is demonstrated by a recent study by Orom et al., which found a significant association between men who are knowledgeable about prostate cancer and treatment-related side effects at the time of decision making and quality of life six months post-treatment. (184) Similarly, Albkri et al. determined that the primary reason for decision regret amongst patients with localised prostate cancer was incomplete pre-treatment counselling, including information about prostate cancer (40%) and treatment-related urinary sequelae (34%).(185)

Unfortunately, reliable information regarding the impact of prostate cancer treatment on urinary and sexual function is not always readily available for patients. An international sexual health guideline has recently been published to develop a framework for shared decision-making between physicians, patients, and their partners. (186) The guideline promotes a more holistic biopsychosocial and culturally sensitive approach to survivorship amongst patients with prostate cancer. (186)

Therefore, for patients with localised prostate cancer, accurate knowledge of the incidence of late genitourinary toxicity requiring surgical procedures or hospital admissions would enhance patient-centred decision-making concerning treatment selection. (187)

Problem Definition

Recent studies have shown that radiation-induced pelvic toxicity often presents to urology centres for management. (188, 189) However, the incidence of late genitourinary toxicity following intensity-modulated radiotherapy (IMRT) remains unclear.(148-150, 190-193). The introduction of IMRT is thought to reduce toxicity compared to Three-Dimensional Conformal Radiotherapy (3D-CRT) because of the increased treatment conformality. (140, 141) Earlier review studies, which compared the efficacy and toxicity associated with IMRT against 3D-CRT and radical prostatectomy, were limited by a lack of randomisation and prospective analyses, the inclusion of retrospective studies and conference data abstracts, and shorter minimum follow-up periods, which may have underestimated the incidence of late genitourinary toxicity. (19, 141) More high-quality studies are required to determine the late genitourinary toxicity rates because the wide variation in treatment techniques, radiotherapy doses, and late toxicity scoring systems makes interpretation of the results difficult. (19, 140-147) Hence the incidence of late genitourinary toxicity following IMRT remains poorly characterised. (148-150)

Furthermore, there is limited high-quality data identifying predictive factors for late genitourinary toxicity after radiotherapy. Currently, the literature mainly consists of single-center observational studies of RT complications but lacks review studies grouping the data. Only a few studies have successfully validated predictive models using dose-volume data to predict late genitourinary toxicity. (181, 194) The development of dose-volume effect predictive models can assist clinicians in selecting more suitable candidates for the different prostate cancer treatment groups based on their probability of developing severe radiotherapy toxicity. Furthermore, there are no recognised normal tissue-sparing dose-volume histogram (DVH) criteria to limit the risk of genitourinary toxicity from prostate radiotherapy.

Recent studies report a strong association between Transurethral resection of the prostate (TURP) and radiotherapy toxicity amongst men with prostate cancer and concurrent bladder outlet obstruction. (195-198) The prospective cohort study by Zapatero et al. of men with localised (T1c-T3b) prostate cancer treated with dose-escalated 3DCRT (n=229) determined that TURP was a strong (RR 2.8, $p = 0.026$) independent predictor of late grade ≥ 2 haematuria in multivariable analysis, after adjusting for androgen deprivation and dosimetric factors ($p > 0.05$). This study's strong association between TURP and toxicity may be due to the lack of stratification of patients with bladder outlet obstruction and TURP. In particular, the study does not include a comparison of patients with bladder outlet obstruction who did not undergo TURP prior to EBRT.

Similarly, recent studies have reported a strong association between diabetes and the development of prostate radiotherapy-related toxicity. (194, 199) The ability of normal tissue to self-repair after sustaining radiation damage is heavily reliant on its vascular supply. A compromised vascular supply to the irradiated organ could affect the perfusion to the damaged tissue and lead to delay or failure in the repair process. (199) Chronic diabetes leads to structural changes to the microvasculature, including advanced atherosclerosis, arteriolar obliteration, and capillary hyalinisation, which can significantly reduce tissue perfusion. (200) In addition, patients with diabetes have increased blood viscosity and glycosylated haemoglobin, with an altered oxygen-haemoglobin dissociation curve, further impairing the perfusion to already compromised tissues (201). The association between diabetes and late treatment-related genitourinary toxicity was highlighted by the retrospective study by Herold et al. involving (N=949) patients with prostate cancer treated with curative-intent 3DCRT (median 72Gy) at Fox Chase Cancer Center. The study reported that type II diabetes mellitus was the only independent predictor of late grade 2 GU toxicity ($p = 0.0110$), in stepwise multivariable analysis, after adjustment for age, dose, rectal blocking, and field size

Smoking has also been identified as a potential risk factor for the development of radiation-induced toxicity. The importance of smoking status was demonstrated by Solanki et al. in a study of men with prostate cancer (n=633) undergoing definitive EBRT between 1988-2008, involving multivariable regression in a Cox proportional hazards model, which determined a positive association with current smoking status and late RTOG grade ≥ 2 genitourinary toxicity (HR 1.45, $p < 0.02$), but which lost significance when divided into current versus prior versus never smokers ($p=0.34$).(202) However, a recent study by Steinberger et al. involving patients with localised prostate cancer (n= 2358) treated with EBRT (median 81Gy) between 1988-2005 reported a statistically significant increased risk of CTCAE GU toxicity amongst both current (HR 1.8, $p = 0.002$) and former smokers (HR 1.45, $p = 0.001$) in multivariate analysis using a Cox regression model.(203)

Other suspected predictive factors include obesity (138) (204) (138) (204), hypertension (205), anticoagulation (194), abdominopelvic surgery (206), and hormonal therapy.(110, 196, 207-211). A recent review by Coates et al. of predictive models for radiation-induced toxicity in men with prostate cancer has highlighted new trends involving the integration of dosimetric and genetic factors using machine learning techniques to predict toxicity. (94)

Aims and Objectives

Based on the current state of knowledge in this field, the following aims will be addressed in this thesis.

Primary Aims

To determine through systematic review and meta-analysis the long-term (60-month) incidence of genitourinary toxicity (RTOG grade ≥2, CTCAE grade ≥2, haematuria, urinary retention, and urinary incontinence) in patients with localised prostate cancer treated with IMRT without nodal irradiation.

To prospectively determine the burden of treatment associated with late genitourinary toxicity following pelvic radiotherapy at a real-world tertiary community-level institution over 12 months.

To determine the 10-year cumulative incidence of treatment-related genitourinary toxicity following prostate EBRT patients with localised prostate cancer at a population level.

To develop, assess, and validate a novel model to predict genitourinary toxicity using pre-treatment clinical factors for decision-making regarding treatment modality.

To determine and compare the 10-year cumulative incidence of first and recurrent hospital admissions (overall, genitourinary, gastrointestinal) in patients with localised prostate cancer following EBRT or radical prostatectomy at a population level.

To describe five-year Expanded Prostate Cancer Index Composite Patient Reported Outcomes post primary curative intent EBRT alone for localised prostate cancer and to compare outcomes against patients treated with radical prostatectomy.

Secondary Aims

To quantify through systematic review the number of studies reporting very long-term (120-month) follow-up endpoints, time to genitourinary toxicity event analysis, predictive factors, or economic evaluation.

To prospectively compare the volume and severity of toxicity amongst patients with prostate cancer who underwent radiotherapy less than or greater than five years from the date of recorded presentation at a tertiary community-level institution over 12 months.

To describe the characteristics of patients who develop genitourinary toxicity, identify the number and type of admissions and procedures required and explore clinical factors predictive of genitourinary toxicity at a population level.

To determine the clinical utility of the model used to predict genitourinary toxicity and present it for use in the pre-treatment clinical patient counselling setting.

To compare the 10-year incidence of genitourinary, gastrointestinal, and specific pelvic toxicities (i.e., haematuria, urinary retention, and urinary incontinence) in patients with localised prostate cancer following EBRT or radical prostatectomy at a population level

To describe characteristics of patients with evaluable PROMS post primary curative intent EBRT alone for localised prostate cancer and to compare outcomes against patients treated with radical prostatectomy and to perform subgroup analysis on a cohort of patients treated using contemporary techniques.

Significance

The overall thesis provides a unique, comprehensive description, analysis, and comparison of genitourinary toxicity following prostate EBRT. While late toxicity following radiotherapy is thought to be common, it remains poorly understood. The cumulative incidence of GU toxicity after five years following radiotherapy is unclear from recent RCTs. The burden of treatment at a state-population level remains poorly characterised. There are no models to predict the hospitalisation for GU toxicity based on patient pre-treatment clinical factors. Few studies compare five-year patient-reported outcome measurements (PROMS) amongst patients with localised prostate cancer treated with surgery or EBRT using contemporary techniques. Each chapter of the thesis contains a novel contribution to the literature relating to pelvic toxicity after radiotherapy.

Firstly, the systematic review presents the first consolidated literature review and meta-analysis on long-term genitourinary outcomes in patients with prostate cancer treated with primary IMRT.

Secondly, the prospective single-institution study provides a novel assessment of the burden of treatment associated with GU toxicity following pelvic radiotherapy based on a broad range of hospital encounters from the outpatient clinic to the operating room. The subgroup analysis of patients with prostate cancer determined a significantly higher volume of patients with late GU toxicity occurring ≥ five years after radiotherapy and higher RTOG scores than reported in other prospective studies.

Thirdly, the population-level cumulative incidence study of treatment-related genitourinary complications is one of few internationally and the first in Australia. Similarly, this is the first Australian study to determine the volume of admissions and urological procedures for managing radiotherapy treatment-related genitourinary complications at a population level.

Fourthly, the study predicting post-radiation GU hospital admission in patients with localised prostate cancer is the first to develop a validated data-driven predictive model using only pre-treatment clinical characteristics. In addition, this was also the first predictive model for genitourinary toxicity requiring hospitalisation to include a nomogram and decision curve analysis.

The fifth study compares hospital admission amongst men with localised prostate cancer after EBRT or RP that accounts for recurrent events. In addition, it provides the first assessment of recurrent hospital admissions amongst patients treated with either EBRT or RP, adjusted for age and comorbidity.

Finally, the PROMS study represents the first prospective population-level study to compare EPIC-26 scores amongst patients with clinically localised prostate cancer treated by either RP or EBRT using contemporary techniques (treatment date from 2010 onwards) with five years of follow-up data.

Competing Interests

The authors declare that they have no competing interests.

Audience

The target research audience for this study is primarily clinicians at tertiary centres who manage patients with genitourinary toxicity after external beam radiotherapy. Apart from Urologists and Radiation Oncologists, patients who develop treatment-related genitourinary toxicity are frequently managed by Emergency Care Physicians, Oncology and General Medical Physicians, and, less commonly, by intensive care physicians. Specialist nursing and allied health staff, including pelvic floor physiotherapists, also have a crucial role in managing patients with treatment-related genitourinary toxicity.

Organisation

The research will be organised as follows:

Chapter 1: Introduction

Chapter 2: Protocol for a systematic review of Long-term genitourinary toxicity following curative intent intensity-modulated radiotherapy for prostate cancer

Chapter 3: Long Term Genitourinary Toxicity Following Curative Intent Intensity-Modulated Radiotherapy For Prostate Cancer: A Systematic Review and Meta-analysis.

Chapter 4: Genitourinary toxicity following pelvic radiotherapy: A prospective pilot study

Chapter 5: Incidence of Genitourinary Complications following Radiation Therapy for Localised Prostate Cancer

Chapter 6: The Predictive Factors for Post Irradiation Genitourinary complications in patients with prostate cancer.

Chapter 7: Cumulative incidence and prediction of treatment-related complications requiring hospital admission amongst patients with localised prostate cancer

Chapter 8: Comparison of Patient-Reported Outcomes Measures in Patients with Localised Prostate Cancer Following External Beam Radiotherapy or Radical Prostatectomy.

Chapter 9: Discussion and Conclusion

Conclusion

This introductory chapter has revealed the thesis's scope and highlighted the gap in the current literature regarding treatment-related toxicity in men with clinically localised prostate cancer. This thesis will examine an important issue regarding the adverse events experienced by patients with clinically localised prostate cancer who undergo curative intent local treatment with either EBRT or radical prostatectomy. There are many treatment options for prostate cancer, including surgical and radiation modalities. Patients with prostate cancer who undergo radiotherapy are at risk of developing significant treatment-related adverse effects. This work systematically determines the incidence, burden of treatment, and prediction of these treatment-related adverse effects.

Chapter 2: Long Term Genitourinary Toxicity Following Curative Intent Intensity-Modulated Radiotherapy for Prostate Cancer: A Systematic Review Study Protocol

Rowan David, ‡ †

Jason Lee, MS, FRACS (Urol) ‡ †

Arman Kahokehr, PhD, FRACS (Urol) ‡ ^

David Watson, PhD, FRACS ‡

John Leung, PhD, FRANZCR

Michael E. O'Callaghan, PhD ‡ † ¶^

‡ Flinders University, Bedford Park South Australia.

† Department of Urology, Flinders Medical Centre, SA Health, Australia.

¶South Australian Prostate Cancer Clinical Outcomes Collaborative

^ University of Adelaide, Discipline of Medicine, Freemasons Foundation Centre for Mens Health

Abstract

Background. Radiotherapy is a widely accepted curative treatment option for prostate cancer. Post-radiation late genitourinary toxicity is thought to be common, but the evidence supporting this with newer radiotherapy techniques, such as intensity-modulated radiotherapy is mixed.

Purpose. To identify, through a systematic review, the incidence of late genitourinary complications following curative intent intensity-modulated radiotherapy in patients with localised prostate cancer, as recorded by institutions and reported in Patient Reported Outcome Measures. The primary outcome to be assessed will be the cumulative incidence of reported Radiation Therapy Oncology Group (RTOG) Grade≥ 2 late genitourinary toxicity at 60-months follow-up. The secondary outcomes to be determined include the reported incidence of National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Grade≥ 2 late genitourinary toxicity events at 60-months, the presence of time to event analysis, predictive factor analysis and economic analysis, where available in the included articles.

Methods and Materials. We will systematically search MEDLINE, EMBASE and Cochrane Databases from January 2008 to January 2019 for published prospective original articles involving cohort studies, randomised and non-randomised control trials. The literature review will be performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Discussion. The true incidence of post-irradiation late genitourinary complications is controversial. Radiotherapy injuries can remain asymptomatic for a long time, and the difficulty in accurately recording these long-term adverse effects is frequently reported in the literature. Patient counselling prior to prostate radiotherapy treatment is important and may be improved by a better understanding of the incidence of late genitourinary toxicity. Similarly, the predictive factors for genitourinary complications remain unclear and there are few multi-institutional studies involving predictive modelling. A better understanding of these factors can help guide allocation of patients to treatment groups based on their probability of severe radiotherapy toxicity to mitigate late toxicity risk.

Trial registration:

PROSPERO – Registration Number: CRD42019133320

Keywords:

“prostate cancer”, “radiotherapy”, “radiation therapy”, “external beam radiotherapy”, “genitourinary complications”, “urethral stricture”, “bladder neck obstruction”, “radiation cystitis”, “urinary retention”, “urinary incontinence”, “erectile dysfunction”, “bladder neoplasm”

Abstract Word Count: 299

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Background

Prostate cancer is the second most common form of cancer affecting men worldwide.(10) The majority (94%) of patients with prostate cancer have curable localised disease.(17) The treatment options for localised prostate cancer include active surveillance, surgical treatment or radiation therapy. Currently, there is limited evidence to suggest that any treatment option for localised prostate cancer has superior oncological outcomes compared to the other modalities. However, each intervention is associated with a different side effect profile and subsequent impact on the patient's health-related quality of life.(135) Patient's preference and decision-making regarding intervention options is often based upon these treatment-related adverse events.(166) Radiotherapy is a commonly utilised weapon in the therapeutic armamentarium for localised prostate cancer. Radiation therapy to the prostate can be delivered by external beam radiation therapy and/or brachytherapy. The high five-year survival rates (83.4%) following curative intent radiotherapy for localised disease leaves a large cohort of men at risk for long-term adverse effects of their cancer treatment.(18) It is widely accepted that genitourinary complications have a tendency to accumulate and progress during a 15 year period after radiotherapy treatment.(212) Gardner et al. in reported a 59% 15-year incidence of grade ≥ 2 genitourinary toxicity after 77.4 Gy 3D-CRT in patients with prostate cancer, demonstrating that late toxicity may be underestimated by an inadequate duration of follow-up. Despite changes in radiation planning and delivery methods which have aimed to improve the therapeutic ratio of cancer control, some patients may still suffer long term genitourinary sequela.(95, 96) Intensity-modulated radiotherapy reduces the dose to normal tissues and therefore aims to decrease toxicity and improve quality of life.(112) However, the incidence of late genitourinary toxicity following intensity-modulated radiation therapy is controversial and poorly characterised. We hypothesise a large burden of treatment for these late adverse effects because of the high prevalence of localised prostate cancer and the high utilisation of curative intent radiotherapy.

The primary aim of this study is to report the incidence of late Radiation Therapy Oncology Group (RTOG) Grade ≥ 2 genitourinary toxicity at 60-months following curative intent intensity-modulated radiotherapy in patients with localised prostate cancer. We will include adverse outcomes prospectively recorded by treating institutions as well as by Patient Reported Outcome Measures (PROMS).

Our secondary aims are to:

1) Determine the incidence of National Cancer Institute Common Terminology Criteria Adverse Events (CTCAE) Grade ≥ 2 genitourinary toxicity at 60-months.

2) Report the inclusion of specific genitourinary complications, including haematuria, urinary incontinence and urinary retention.

3) Quantify the number of studies reporting predictive factors or predictive models associated with the development of late post-irradiation genitourinary complications.

4) Quantify the number of studies that include economic evaluation, including any studies of cost burden, cost-utility or cost efficacy.

5) Quantify the number of studies that include time to event analysis.

6) Quantify the number of studies that include a RTOG or CTCAE Grade ≥ 2 genitourinary toxicity at a 24 or 120-month endpoint.

The RTOG and National Cancer Institute Common Terminology Criteria Adverse Events (CTCAE) were selection as they can infer requirement for hospitalisation or intervention.

Methods/Design

Search Strategy

Databases searched include MEDLINE, EMBASE and Cochrane from January 2008- 2019. The systematic literature search was conducted in collaboration with an experienced research Librarian from the Medical Library at Flinders University. Example key words and indexing terms used included the following:

Disease-specific terms: prostate cancer, prostate neoplasm and prostate malignancy;

Treatment-specific terms: radiation, radiation therapy, external beam radiotherapy, intensity-modulated radiotherapy;

Outcome-specific terms: haematuria, radiation cystitis, bladder neck contracture, urethral stricture, urinary retention, urinary incontinence, urethral fistula, erectile dysfunction and secondary primary bladder cancer.

Full details of the search strategy are included in Supplementary Material 1 (available online at https://www.crd.york.ac.uk/PROSPEROFILES/133320_STRATEGY_20190804.pdf)

The systematic literature review protocol developed for this study was registered with PROSPERO, an international prospective systematic review registry, prior to the commencement of searches: CRD42019133320

The protocol can be accessed at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=133320. For the reporting of this systematic review and meta-analysis we will follow Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).(213) The systematic review protocol was updated on PROSPERO in 2022 to include studies published up to and including 2021.

Inclusion Criteria

Accepted articles will be considered eligible for inclusion if they meet the following criteria:

(1) Population: Patients with localised biopsy proven prostate adenocarcinoma (T1-T2, according to American Joint Committee on Cancer);

(2) Intervention: Curative intent intensity-modulated external beam radiotherapy.

(3) Outcome: Late genitourinary complications after prostate radiation, as defined as 60-month following IMRT. We will include prospective studies involving institutional data and Patient Reported Outcome Measures (PROMS). We will include toxicity scoring systems that are predictive for hospitalisation, including Radiation Therapy Oncology Group (RTOG), Common Terminology Criteria Adverse Events (CTCAE), Late Effects Normal Tissue Task Force – Subjective, Objective, Management, Analytic (LENT-SOMA). The rates of haematuria, radiation cystitis, bladder neck contracture, urethral stricture, urinary retention, urinary incontinence, urethral fistula, erectile dysfunction and secondary primary urological cancer, where available will be included.

(4) Study Type: Articles written in the English language and published from January 2008. This date was selected because it will allow comparison of outcomes associated with recent advancements in technology and dosimetry. We will only include prospective studies.

Exclusion Criteria

(1) Population: We will exclude men with non-adenocarcinoma prostate cancer, non-localised prostate cancer (stages T3 and T4 according to American Joint Committee on Cancer), metastatic prostate cancer and those who do not have prostate cancer.

(2) Intervention: We will exclude four field box, three dimensional conformational, stereotactic beam, proton beam and brachytherapy. We will exclude studies that did not specify the type of RT or included other prostate cancer treatments, such as prostatectomy, cryotherapy or high-intensity focused ultrasound therapy.

(3) Outcome: We will exclude studies that do not report 60 month-endpoints. We will exclude toxicity scoring systems that are not predictive for hospitalisation, such as the International Index of Erectile Function (IIEF), International Prostate Symptom Score (IPSS), and Sexual Health Inventory for Men (SHIM). Where PROMS are the outcome, studies which do not report baseline incidence levels will be excluded.

(4) Study Type: We will exclude studies that are published before January 2008. We will exclude retrospective studies. We will exclude studies published in a language other than English, case reports, case series (</= 10 participants), non-human studies, and non-primary studies (book chapters, guidelines, editorials, letters, expert input, conference abstracts, grey literature).

Study Selection

The included articles from the literature search will be reviewed in three consecutive phases. One researcher (RD) will screen titles and abstracts for the first pass. The second pass will involve a two-author (RD, MOC) review of the full texts. Finally, the reference lists of the selected articles and those

of previous systematic reviews will be reviewed to identify other possible studies that could be included. The coding for inclusion and exclusion criteria will be applied and recorded for each stage. Uncertainty will be addressed with the assistance of a senior reviewer (DW).

Data Collection Process and Data Items

After full-text review, data extraction will be undertaken by two reviewers (RD, AB). Data will be extracted using a pre-defined list generated on Covidence. Completion of the data extraction will be performed by one author (RD) with independent verification performed by other authors (MOC or AK). Information for extraction will include manuscript identifiers, including first author names, title of studies, year of publication and location of study (US, Canada, Asia, Europe, Australia). We will record study design, median follow-up (months), sample size at baseline and at each point of follow-up. We will collect clinical characteristics, including patient age (years), PSA at diagnosis, ISUP grade, risk classification score and clinical stage, percentage of patients on Androgen Deprivation Therapy (ADT) and history of transurethral prostatectomy (TURP). We will also record radiation dosage (total dose/number of fractions [daily fractionated dose], equivalent dose [EQ D2]). We will collect outcome information including toxicity criteria, respective severity grading score, number of adverse late genitourinary events and whether these events were recorded in by institutions or patient reported outcome measures. The data regarding the severity of post-irradiation genitourinary complications will be aggregated and the instrument used will be reported. Several different scales are used to assess outcomes such as radiation cystitis and thus we will have selected the scoring systems which infer the need for hospitalisation.

The text appraisal, quality assessment and data extraction using standardised forms will be performed using the online tool “Covidence”.

Quality Assessment

Quality assessment will be performed by 2 reviewers (RD, MOC, JL or AK). We will report consistency in reported data, including whether data is presented with hazard ratios compared to controls or absolute costs. For randomised control trials, we will use the Cochrane Handbook Table 8.5 to assess risk of bias as either high risk, low risk, or unclear risk. For non-randomised studies, we will use the Newcastle-Ottawa scale instrument to assess bias on three broad areas, including group selection, group comparability and the ascertainment of the exposure. For studies involving predictive modelling, we will use the Quality in Prognosis Studies (QUIPS) tool for assessing risk of bias. Discrepancies between the reviewers until consensus has been reached.

Outcome Reporting and Analysis

We will report the incidence of toxicity as recorded by hospital institutional data and patient-reported outcome measures. The main outcome we will assess is the incidence of late genitourinary complications after prostate radiotherapy at 60 months post treatment. We will use meta-analysis techniques to describe the cumulative incidence of post-radiation genitourinary complications as stratified by adverse event grading criteria. Heterogeneity amongst studies will be evaluated using I^2 statistic method. Heterogeneity will be considered statistically significant when $I^2 > 50\%$. We will use a random effect model (DerSimonian-Laird method) to account for variation in adverse events due to differences in study populations, questionnaires and methods. We will not include studies with poor follow-ups that utilise estimators. We will evaluate to possibility of publication bias by using Begg's funnel plot, Begg's test and Egger's test. Forest plots will be generated showing the summarised findings and 95% Confidence Intervals estimated in the meta-analysis.

Subgroup Analysis

We will compare outcomes across two other end points at 24 months and 120 months following radiotherapy commencement. Where available, we will extract reports of specific genitourinary complications, including haematuria, radiation cystitis, bladder neck contracture, urethral stricture, urinary retention, urinary incontinence, urethral fistula, erectile dysfunction and secondary primary bladder cancer. We will also analyse the number of studies which report predictive factors, health economics or time to adverse event and collect a 'yes/no' answer for inclusion.

Discussion

Radiotherapy can cause a range of genitourinary complications, including erectile dysfunction, urethral stricture, bladder neck contracture, urinary retention, urinary incontinence, radiation cystitis, fistulae and secondary primary bladder neoplasm. Sexual dysfunction remains the most common complication amongst prostate cancer survivors and contributes to the most significant health-related quality of life burdens in all of cancer survivorship.(163) Erectile dysfunction is a well-recognised and challenging adverse effect after prostate radiation treatment, with rates varying from 6 to 84% following external beam radiotherapy and from 0 to 51% after brachytherapy.(164, 165) Patients can also develop radiation-induced urethral strictures and bladder neck contractures which can lead to bothersome obstructive voiding symptoms that can negatively impact their quality of life. A recent systematic review by Awad et al in 2016, involving 16,129 patients who underwent either EBRT, BT or a combination, found that the prevalence rate of urethral stricture was 2.2% (95% confidence interval, CI 1.9-2.6%) over a median follow-up time of 4 years (interquartile range, IQR 2.7-5).(214) The risk of urinary retention following newer radiotherapy techniques, such as hypofractionated radiotherapy, has yet to be fully evaluated.(215) The recent trend towards dose escalation and hypofractionation may have a role in increasing the rates of post-treatment urinary incontinence, which can affect patients quality of life.(216, 217) The true incidence of radiation cystitis has been a matter of controversy, with reported estimates ranging from 2.6% to 12.1%.(159-161) Radiation cystitis represents a spectrum of presentations, which can include pain, haematuria and increased urinary frequency. Radiation-induced secondary primary bladder cancer is well described in the literature after curative intent radiotherapy for prostate cancer. Our study aims to contribute to the literature with an evaluation of the incidence of late genitourinary complications following treatment with intensity-modulated radiotherapy. We further aim to infer from the selected scoring systems the number of reported cases requiring hospitalisation.

Interstudy comparisons of genitourinary toxicity are challenging because of the several different scoring systems utilised in the literature. The LENT-SOMA considers objective and subjective endpoints separately. The CTCAE does not differentiate between acute and late effects and can be ambiguous, especially in grading of urinary incontinence. The RTOG score for genitourinary complications is also a commonly utilised tool in many of the prospective multicentre studies. Similarly, Health-related quality of life is an increasingly important end point in prostate cancer care. There are several health-related quality of life reporting systems that are commonly described in the literature. The Expanded Prostate Cancer Index Composite (EPIC)-26 is a robust instrument that facilitates a comprehensive assessment of prostate cancer-related health-related quality of life.(218) The American Urological Association Symptom Index (AUA) is a clinically sensible, reliable, valid, responsive and practical tool also frequently utilised in the literature.(219) The Sexual Health Inventory for Men (SHIM) questionnaire is a widely used, multi-dimensional self-report instrument for the evaluation of male sexual function.(220, 221)

A better understanding of predictive factors may be useful in decision making regarding treatment modality.(222) Similarly, predictive models can also be developed and will be a helpful tool for patient counselling regarding treatment options.(223) Analyses of cost-effectiveness are of increasing importance because of the escalating costs associated with technological improvements in the therapeutic armamentarium for prostate cancer. A recent systematic review by Becerra et al in 2015, found limited evidence supporting the relative cost-effectiveness of the different treatment modalities for men with localised prostate cancer, highlighting the need for further studies.(224)

Authors Declarations

Author's Contributions

All authors were involved in designing and reviewing the study protocol. RD and MOC defined the search strategy and data extraction table. RD was the major contributor in writing the manuscript under the supervision of MOC, who is the guarantor of the review. All authors read and approved the final manuscript.

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Chapter 3: Long Term Genitourinary Toxicity Following Curative Intent Intensity-Modulated Radiotherapy For Prostate Cancer: A Systematic Review And Meta-Analysis

Rowan David, MBBS ‡ †

Alex Buckby, MBBS †

Arman A. Kahokehr, BHB, MBChB, PGDMSc, PhD, FRACS ‡ ^

Jason Lee, MS, FRACS (Urol) ‡ †

David I. Watson, PhD, FRACS ‡

John Leung, PhD, FRANZCR ¥ ǂ

Michael E. O'Callaghan, PhD †‡ ¶^

ǂ College of Medicine and Public Health, Flinders University, Bedford Park South Australia.

† Department of Urology, Flinders Medical Centre, SA Health, Australia.

¥ GenesisCare, Adelaide, Australia

¶ South Australian Prostate Cancer Clinical Outcomes Collaborative

^ University of Adelaide, Discipline of Medicine, Freemasons Foundation Centre for Men's Health

Abstract

Background. Recent studies have shown that radiation-induced pelvic toxicity often requires urological consultation. However, the 10-year incidence of genitourinary toxicity following intensity-modulated radiotherapy (IMRT) amongst patients with localised prostate cancer remains unclear. Hence, we conducted a systematic review and meta-analysis to determine the incidence of late genitourinary toxicity relying on Radiation Therapy Oncology Group (RTOG) and Common Terminology Criteria for Adverse Events (CTCAE) grade as well as the incidence of specific genitourinary toxicity. Secondary objectives involved quantifing the number of studies reporting 120-month follow-up endpoints, time to event analysis, predictive factors or economic evaluation.

Methods. Articles published from January 2008 - December 2021 describing prospective studies were systematically searched in MEDLINE, EMBASE and Cochrane (PROSPERO protocol CRD42019133320). Quality assessment was performed by use of the Cochrane Risk of Bias 2 Tool for RCTs and the Newcastle Ottowa Scale for non-RCTs. Meta-analysis was performed on the 60-month incidence of RTOG and CTCAE Grade ≥2 genitourinary toxicity, haematuria, urinary retention and urinary incontinence.

Results. We screened 4721 studies and six studies met our inclusion criteria. All included studies involved normofractionation, three included a hypofractionation comparator arm and none involved nodal irradiation. The pooled 60-month cumulative incidence of RTOG and CTCAE Grade ≥2 genitourinary toxicity were 17% (95% CI: 5-20%, n=678) and 33% (95% CI: 27-38%, n=153), respectively. The pooled 60-month cumulative incidence of Haematuria was 5% (95% CI: -4-14%, n=48), Urinary incontinence 12% (95% CI: 6-18%, n=194), Urinary retention 24% (95% CI: 9-40%, n=10).

One study reported time to event analyses, one reported predictive factors, no studies reported economic analysis or 120-month toxicity. There was considerable heterogeneity amongst the studies.

Conclusion. There are few high-quality studies reporting 60-month toxicity rates after IMRT. Conservative estimates of 60-month toxicity rates are high and there is need for longer follow-up and consistent toxicity reporting standards.

Keywords: “prostate cancer”, “radiotherapy”, “radiation therapy”, “external beam radiotherapy”, “genitourinary complications”, “urethral stricture”, “radiation cystitis”

Abstract Word Count: 300

Manuscript Word Count: 2428

Background

Recent studies have shown that patients with radiation-induced pelvic toxicity often present to urology centres for management.(188, 189) However, the incidence of genitourinary toxicity five to ten years following intensity-modulated radiotherapy (IMRT), remains unclear.(190-193) The introduction of IMRT is thought to achieve a reduction in toxicity compared to Three-Dimensional Conformal Radiotherapy (3D-CRT) because of the increased treatment conformality.(140, 141) However, earlier review studies, which compared the toxicity associated with IMRT against 3D-CRT were limited by a lack of randomised prospective analyses as well as the inclusion of retrospective studies and shorter minimum follow-up periods, which may have underestimated the incidence of late genitourinary toxicity.(19, 141, 225) More high-quality studies are required to determine the late genitourinary toxicity rates because of the wide variation in radiotherapy techniques and dose regimes.

In addition, the numerous disparate late toxicity scoring systems makes interpretation of the results difficult due to lack of consistency and accuracy.(19, 140-147) The Radiation Therapy Oncology Group (RTOG) is one of the dominant scoring systems reported in the oncology literature, however has undergone numerous iterations to improve its accuracy. Whilst the Common Terminology Criteria for Adverse Event (CTCAE) is promoted as the comprehensive standard for reporting treatment-related adverse events in oncological care, it is often underutilised in trials. Hence the incidence of late genitourinary toxicity following IMRT remains poorly characterised.(148-150)

The primary aim of this systematic review and meta-analysis was to determine the 60-month incidence of genitourinary toxicity relying on RTOG and CTCAE grade and the incidence of specific genitourinary toxicity, including haematuria, urinary retention and urinary incontinence in patients with localised prostate cancer treated with IMRT without nodal irradiation. Secondary objectives involved quantifying the number of studies reporting 120-month follow-up endpoints, time to genitourinary toxicity event analysis, predictive factors or economic evaluation.

Methods

Evidence Acquisition

Selection Criteria

Accepted articles were considered eligible for inclusion if they met the following criteria:

(1) Population: Patients with non-metastatic biopsy-proven prostate adenocarcinoma (T1-T4, according to American Joint Committee on Cancer).

(2) Intervention: Studies involving curative intent primary external beam intensity-modulated radiotherapy were included. Studies that did not specify the type of radiotherapy used or included other prostate cancer treatments were excluded.

(3) Comparator: A comparator group was not required because of the descriptive nature of the proposed study. However, different radiotherapy techniques, including hypofractionation and image-guided radiotherapy were considered, where reported.

(4) Outcome: Late genitourinary complications after prostate radiation, as defined as 60-month following IMRT. Toxicity scoring systems that are predictive for hospitalisation, including Radiation Therapy Oncology Group (RTOG) and the Common Terminology Criteria Adverse Events (CTCAE) were included. The rates of haematuria, urinary incontinence and urinary retention, where available were included.

(4) Study Type: Prospective studies published between January 2008 and December 2021 were included. This date range was selected because it will allow comparison of outcomes associated with recent advancements in technology and dosimetry. Non-English-original articles, experimental studies on animals, meeting abstracts, book chapters, case reports and cohort studies involving less than 10 patients, reviews, editorials and commentaries were not included in the review.

Search Strategy

A comprehensive search was undertaken to systematically identify literature concerning adverse events following radiotherapy in men with prostate cancer. The following databases were searched: MEDLINE (1950-present), EMBASE (1980-present) and the Cochrane Controlled Trials Register (1991-present).

Both Medical Subject Headings (MeSH) terms and text words were used and terms common to all searches included: prostate cancer; prostate carcinoma; prostatic neoplasms [MeSH]; radiation; radiotherapy; radiation injury; haematuria; bladder neck obstruction; urinary retention; urinary incontinence; erectile dysfunction. Retrospective studies, case cohorts of <10 patients, case reports and conference abstracts were excluded. Studies only published in languages other than English were also excluded.

The review protocol, which includes the search strategy for MEDLINE, (Supplementary 1) was prospectively registered with PROSPERO (available online at https://www.crd.york.ac.uk/PROSPEROFILES/133320_STRATEGY_20220206.pdf). (226) The PRISMA protocol was followed.(Supplementary 2)

Study eligibility

The included articles from the literature search were reviewed in three consecutive phases. One researcher (RD) screened titles and abstracts for the first pass. The second pass involved a two-author (RD, AB) review of the full texts. Finally, the reference lists of the selected articles and those of previous systematic reviews were reviewed to identify other possible studies that could be included. The coding

for inclusion and exclusion criteria were applied and recorded for each stage. Discrepancies were resolved with the assistance of a senior reviewer (MO'C).

Data Extraction and Analysis

Data extraction was independently performed by two authors (RD and AB) according to a preformed standardised template generated using Covidence (Veritas Health Innovation, Melbourne, Australia), an online tool for systematic reviews. We tabulated the study characteristics (author, year, country, baseline sample size, endpoint sample size, median follow-up, setting, design), patient demographics and cancer metrics (age, PSA, tumour score and grade, hormone use status, radiotherapy (fractions and dose) and secondary outcomes (60-month incidence of haematuria, urinary incontinence and urinary retention; whether the studies reported 120-month outcomes, time to event, predictive or economic analysis).

Meta-analysis was performed on the 60-month rates of RTOG or CTCAE late ≥2 genitourinary toxicity, haematuria, urinary retention and urinary incontinence using R studio (Boston, MA 2020). A random-effects model (DerSimonian-Laird method) was selected for the studies reporting genitourinary toxicity, because of the evidence of the heterogeneity in demographic and treatment characteristics amongst the studies. The Q-test and the I^2 statistic method were performed to measure statistical heterogeneity across studies. The Chi-square test with Yates correction was used in the subgroup analysis of hypofractionation and normofractionation. Where appropriate, funnel plots were constructed to assess publication bias.

Quality Assessment

The Cochrane Risk of Bias 2 tool was used for quality assessment for randomised controlled trials. The Newcastle Ottowa Scoring system was used to evaluate the risk of bias for non-RCT studies. The Newcastle Ottowa Scoring scores were adapted for graphical presentation by the following conversion: 2 stars = low risk, 1 star = unclear risk, 0 stars = high risk. Risk of bias analysis was performed using robvis (McGuinness, LA 2019), an online extension of an R-studio package.(227)

Evidence Synthesis

Literature Search

The search yielded 4698 unique references; 4650 were excluded after reviewing the title and abstract. Of the remaining 48 studies, 43 were excluded for reasons listed in Figure 1. One further study which was identified via citation search was included.(Figure 1) Six (0.13%) articles were included for data extraction and meta-analysis. We included one prospective cohort study(228) and five randomised control trials.(229-233) All included randomised controlled trials were phase III trials with parallel groups, of which four compared hypofractionation and normofractionation (Table 1).(230, 233, 234) There were five multi-centre (229-233) and one single-centre study.(228) Studies were from the Netherlands,(229, 230) Australia,(228) France,(231) Canada,(233) and the UK.(232)

Patient Demographics

There was a combined total of 5840 prostate cancer patients treated with curative intent IMRT amongst the included studies. Patient demographic characteristics from the selected studies, including age, tumour stage and grade, prostate-specific antigen, hormonal status, diabetes, and cardiovascular history are summarised in Table 2. The median (range) of sample sizes at baseline was 626 (41-3216). There was a total of 2,244 (38% of the baseline population) patients included at the 60-month follow-up endpoint, with sample size attrition rates ranging from 7-83% between studies (Table 3). Baseline IPSS was not reported in the included studies.

Incidence of Late Genitourinary Toxicity

Five studies reported toxicity with the RTOG scale.(228-230, 232) The pooled 60-month RTOG ≥2 genitourinary toxicity incidence was 17% (95% CI: 5-28%) based on a random-effects model (I^2 98%; Figure 2). The one included study that reported CTCAE ≥2 genitourinary toxicity demonstrated a 60-month incidence rate estimate of 33% (95% CI: 27-38%) based on a fixed-effects model (Figure 2).(231)

Incidence of Specific Genitourinary Toxicity

Three studies reported the rate of haematuria at a 60-month endpoint with a pooled 60-month incidence rate estimate of 5% (95% CI: -4 -14%), based on a random-effects model (I^2 96.73%; Figure 2).(228, 229, 231) Three (60%) studies reported urinary incontinence at 60-month follow-up endpoint, with a pooled 60-month incidence rate estimate of 12% (95% CI: 6-18%), based on a random-effects model (Figure 2).(229-231) One (20%) study reported urinary retention at 60-months, with a 60-month incidence rate estimate of 24% (95% CI: 9-40%), based on a fixed-effects model (Figure 2).(229) One study reported time to event analysis and (232) one reported predictive factors analysis.(230) None of the included studies included economic analysis. (Table 3)

Subgroup Analysis

Three of the included studies compared men with localised prostate cancer treated with either hypofractionated or normofractionated intensity modulated radiotherapy.(230, 233, 234) All three of these studies reported RTOG genitourinary toxicity, with RTOG ≥2 late genitourinary toxicity occurring in 475/3154 (15%) and 378/2050 (18%) of the hypofractionation and normofractionation arms,

respectively. There was no significantly significant difference in RTOG Grade ≥2 genitourinary toxicity at 60-months post-radiotherapy amongst men with localised prostate cancer treated with normofractionation compared with hypofractionation (1.07, 95% CI: 0.91, 1.26, p = 0.41), based on a random effects model. (Figure 3)(230, 233, 234)

Risk of Bias Assessment

Weighted summary bar plots of the studies assessing the incidence rate of late genitourinary toxicity revealed an overall high risk of bias for all studies based on the Cochrane Risk of Bias 2 Tool. A large proportion of the bias was due to the lack of blinding of participants and outcome assessors (Figure 4). For each analysis, there were less than ten included studies, reducing the usefulness of funnel plot presentations to assess publication bias.

Discussion

Our systematic literature review of prospective studies reporting long term urologic complications after radiation therapy treatment for prostate cancer included five articles in a meta-analysis, with a pooled RTOG ≥ 2 incidence of 17% (95% CI: 5-20%). Additionally, the single study included that assessed late CTCAE grade ≥2 genitourinary toxicity reported a 33% incidence (95% CI: 27-38%). These two metrics correlate well, with a reported 10% under-estimation of toxicity as measured by RTOG compared with CTCAE.(235) Our meta-analysis revealed a strong effect size with broad confidence intervals and considerable heterogeneity amongst studies. Overall, the toxicity rates reported likely remain a conservative estimate given under reporting and bias due to lack of blinding in those assessing the outcomes.

This study reports a 5% (95% CI: -4 to 14%) pooled incidence rate estimate of haematuria at 60-months post-IMRT, which is consistent with rates reported elsewhere in the literature.(159-161) The incidence of radiation cystitis remains controversial, with reported estimates ranging from 2.6% to 12.1% amongst mostly low-level evidence studies including retrospective series and conference abstracts, which often lack documentation of toxicity diagnosis and reporting of validated toxicity scoring systems.(159, 160, 236) The current study reports 12% (95% CI: 6-18%) and 24% (95% CI: 9-40%) pooled 60-month rate estimates of urinary incontinence and urinary retention, respectively. Unfortunately, the rate of urinary retention was only reported in one of the included studies, which had a very small sample size (n = 41 at baseline, n = 7 at 5 years post treatment and n= 10 with urinary retention) and is likely overestimated.(229) The need for long term follow-up of lower urinary tract symptoms was highlighted by the recent meta-analysis by Awad et al.,(214) which found that an increase in median follow-up time after prostate EBRT led to a significantly increased risk of developing urethral strictures (OR 0.005, 95% CI 0.0002-0.01, p = 0.041). The predictive factors of radiation-

induced genitourinary complications remain unclear. Currently, the literature consists of observational studies of radiotherapy complications but lacks review studies grouping the data. The cost associated with radiation therapy-related complications also remains poorly described, despite the growing number of global economic comparative evaluations of treatments for localised prostate cancer.(150, 224, 237) Furthermore, the cumulative incidence of treatment-related genitourinary at 120 months was unable to be determined due to lack of reporting in the included trials and may be higher and more severe, given the progressive fibrosis that can develop in patients with radiotherapy-related toxicity.(159) Other recent meta-analyses have also shown no statistically significant differences in late genitourinary toxicity amongst men with prostate cancer treated with hypofractionated radiotherapy compared with conventional radiotherapy.(142, 238)

The current study has several limitations, including a small number of included studies, high heterogeneity between studies and predominant use of the RTOG system, which may miss complications. The meta-analysis was dominated by the inclusion of 3216 (69%) patients from the CHHip trial(234), with the main dose fractionation schedule of 74Gy/37#, which is now outdated. Furthermore, radiotherapy in the CHHiP trial was not routinely delivered with image-guidance and involved larger margins than typically expected.(234) Similarly, most of the included studies use generous margins with unclear standards for IGRT.(228-230, 233) In addition, the PROFIT trial by Catton et al., included an unreported proportion of patients treated with 3DCRT who met the protocol-mandated normal tissue dose constraints. (233) Some relevant trials may have been excluded as they did not meet the inclusion criteria. (239-241) However, the vast majority of these studies were low-level single institution retrospective studies, which are likely to underestimate toxicity given the reliance on physician reported rather than patient reported outcomes. Furthermore, the included studies involved contemporary radiotherapy techniques, and were all prospective and mainly RCTs, with standardised outcome measurements.

This study reports the incidence of complications but does not differentiate toxicity grades or compare to alternative treatment pathways (e.g. radical prostatectomy), as the data was not provided in the included studies. Furthermore, this study does not evaluate the long-term toxicity associated with adjuvant or salvage radiotherapy, which exposes larger portions of adjacent normal tissue to radiotherapy, and which is likely also underreported. This study does not include an exhaustive assessment of genitourinary toxicity and omits quality of life outcomes which may be equally important.(154-158) Whilst the pooled incidence rate is likely an underestimate in aggregate, it may also be an overestimate for patients with a small prostate and low baseline IPSS and those treated with IGRT. While we report a correlation between radiotherapy treatment and the development of symptoms such as haematuria, urinary incontinence and retention over 60-months this association may not be causal. There is a need for a prospective population-level dataset with central registration for patients with confirmed late radiation cystitis, urinary tract strictures and necrotic bladder neck contractures to allow for baseline assessment and formal standardisation.

Conclusion

The current study presents the first consolidated literature review and meta-analysis on long term genitourinary outcomes in patients with prostate cancer treated with primary IMRT. The 60-month incidence of genitourinary toxicity following IMRT provided in the current study exceeds traditional expectations and is likely a conservative estimate. Furthermore, the paucity of high-quality studies reporting late toxicity is concerning. Future studies of radiotherapy techniques should involve longer follow-up and improved toxicity reporting standards.

Author Declarations

Ethical Approval and Consent to participate

The review study does not require ethics approval as it does not involve any participants.

Consent for publication

The findings of the review will be submitted for peer-reviewed publications and presented at scientific meetings.

Availability of supporting data

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors declare that they have no competing interests.

Funding

The authors have no sources of funding to declare.

Author's Contributions

Rowan David: Study conception and design, Acquisition of data, Analysis and interpretation of data, Drafting of manuscript. **Alex Buckby:** Acquisition of data, Analysis and interpretation of data. **Arman Kahokehr:** Acquisition of data, Drafting of manuscript, Critical Revision. **Jason Lee:** Study conception and design, Drafting of manuscript, Critical Revision. **David Watson:** Study conception and design, Drafting of manuscript, Critical Revision. **Michael O'Callaghan:** Study conception and design, Acquisition of data, Drafting of manuscript, Critical Revision.

Guarantor

MOC

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Alexander Jay, Michael Chong, Urology Department, Flinders Medial Centre, Bedford Park South Australia 5042.

Figures

Figure 1. Flow diagram of Evidence Acquisition in a Systematic Review of Late Genitourinary Toxicity in Prostate Cancer Patients Treated with IMRT.

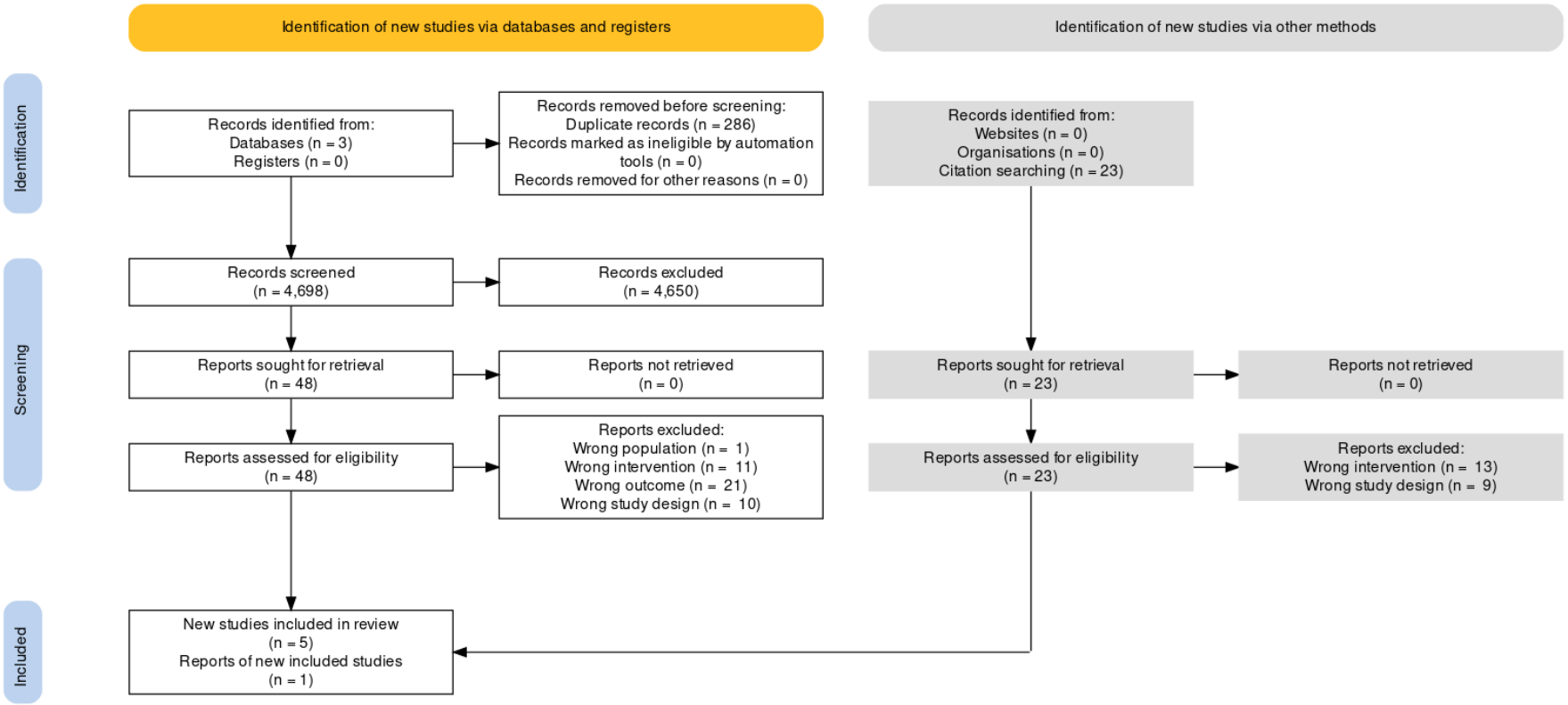


Figure 2. Forrest Plots of Studies Included in the Meta-analysis Demonstrating the 60-month Incidence of RTOG and CTCAE ≥ 2 Toxicity, Haematuria, Urinary incontinence and Retention.

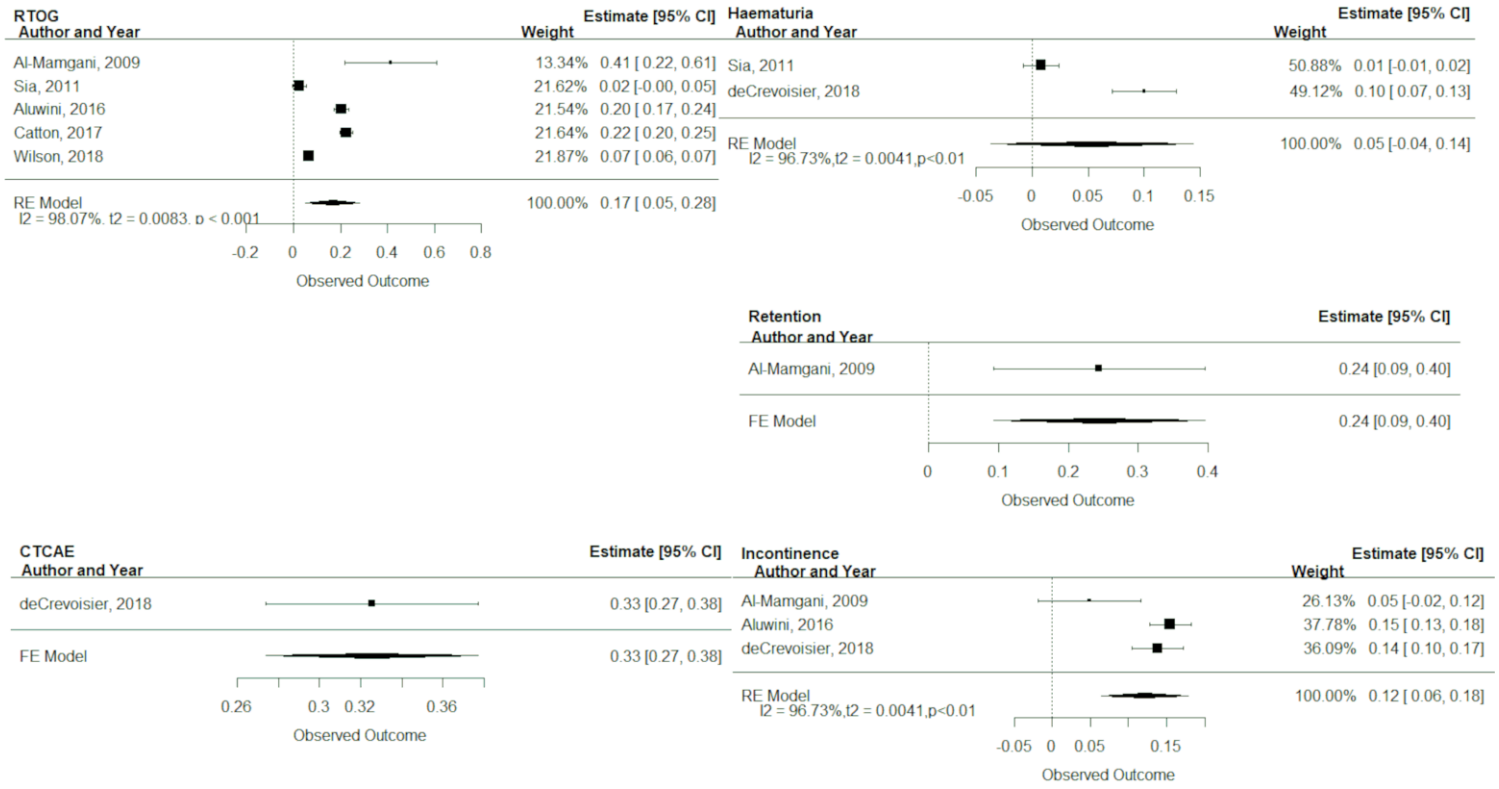


Figure 3. Forrest Plots of Studies Included in the Meta-analysis Comparing the 60-month Incidence of RTOG Amongst Patients Treated with Hypofractionation and Normofractionation Intensity Modulated Radiotherapy.

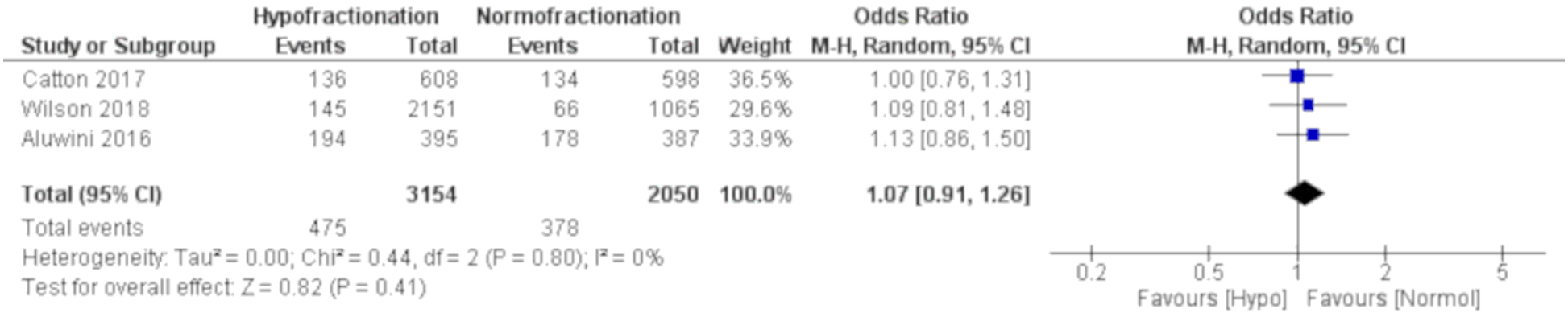


Figure 4. Weighted Summary Bar Plot and Traffic Light Plot for Included RCTs and Non-RCT based on the Cochrane Risk of Bias 2 Tool and Newcastle Ottowa Score, respectively

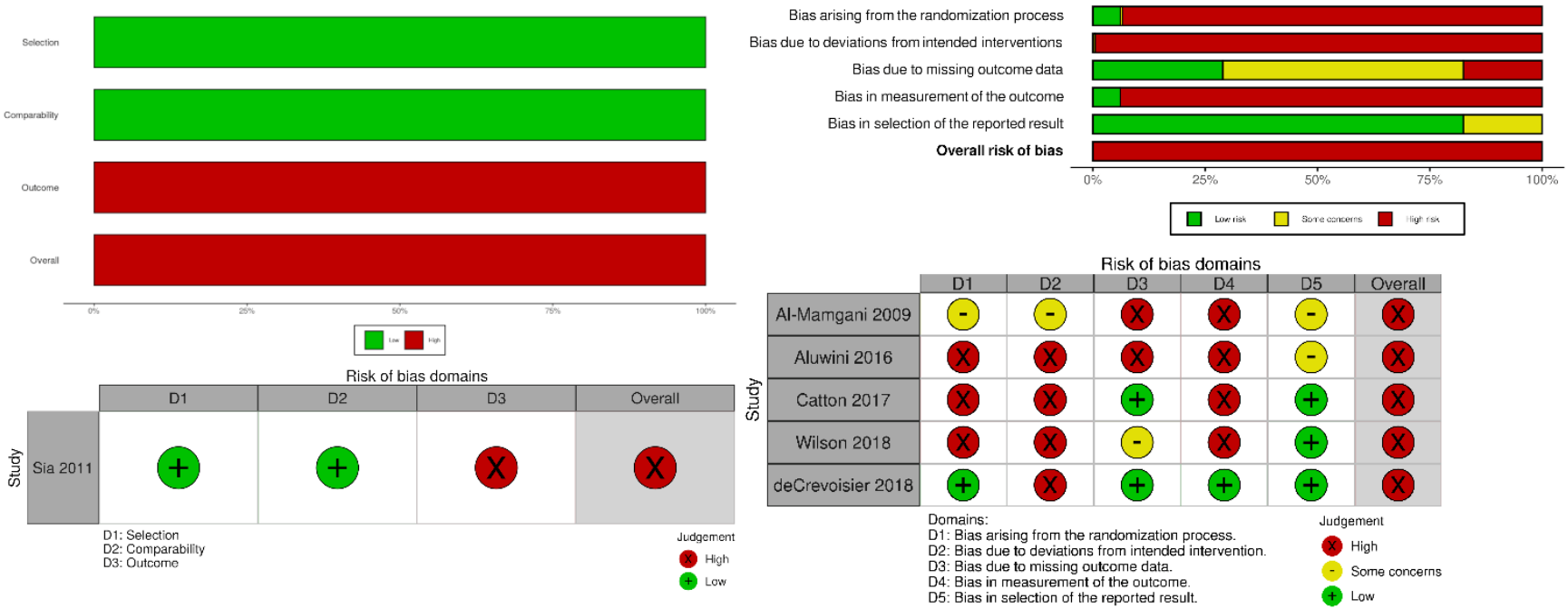
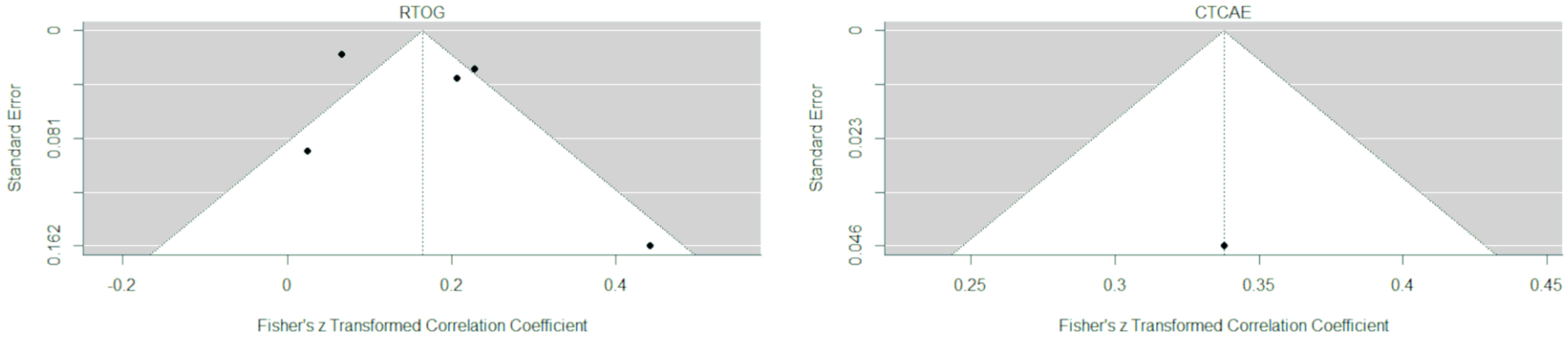


Figure 5. Funnel Plots of Heterogeneity for Studies Included for Meta-analysis of Late RTOG and CTCAE Genitourinary Toxicity Rates



Tables

Table 1. Characteristics of Included Studies

Author, Year, Country	Setting	Trial phase	Intervention model	Arms	Baseline sample, N (%)	Endpoint sample, N (%)	Median follow-up, months
Al-Mamgani (229), 2009, Netherlands	Multi-centre	Phase III	Parallel groups	1.SIB-IMRT (78Gy/39#, no IGRT) 2.SEQ-3DCRT (Excluded)	41 (100%)	7 (17%)	56
Sia(228), 2011, Australia	Single-Center	Prospective cohort study	Single arm	IMRT (74Gy/37#, No IGRT)	125 (100%)	32 (26%)	60
Aluwini(230), 2016, Netherlands	Multi-centre	Phase III	Parallel groups	1.NFRT (78Gy/39#, mostly IGRT) 2.HYPO (64.4GY/19#)	387 (49%) 395 (51%)	97 (25%) 102 (26%)	62

Catton(233), 2017, Canada	Multi-center	Phase III	Parallel groups	1.NFRT (78Gy/39#, IGRT) 2.HYPO (60Gy/20#, IGRT)*	598 (50%) 608 (50%)	396 (66%) 398 (66%)	49
deCrevoisier(231), 2018, France	Multi-centre	Phase III	Parallel groups	1. IGRT daily (78Gy/39#) 2. IGRT weekly (78Gy/39#)	236 (50%) 234 (50%)	437 (93%)	66
Wilson(232), 2018, UK	Multi-center	Phase III	Parallel groups	1. NFRT (74Gy/37#) 2. HYPO (60Gy/20#) 3. HYPO (57Gy/19#)	1065 (33%) 1074 (33%) 1077 (33%)	775 (24%)	72

Gy, Grays; #, Fractions; SIB, simultaneous integrated boost; SEQ, Sequential boost; HYPO, Hypofractionation; NFRT, normofractionation; IGRT, Image guided radiotherapy; CIMRT, Conventional fractionated intensity-modulated radiation therapy; CIMRT, conventional fractionation intensity-modulated radiation therapy

* IMRT was encouraged, although 3DCRT was permitted in this study provided that all protocol-mandated normal tissue dose constraints were met (233)

Table 2. Descriptive Baseline Characteristics of Patients Included in Selected Original Publications Identified by Systematic Review

Study	**Age**	**Clinical T category, N(%)**	**Gleason score, N(%)**	**PSA**	**ADT, N(%)**	**DM, N(%)**	**Smoking**	**Prostate size**	**Baseline IPSS**	**Prior TURP**
Al-Mamgani (229)	Mean (SD): 68.3 (6.1)	T1:13(32) T2:13(32) T3:15(36) T4:0(0)	2-4: 4 (10) 5-7: 29 (70) 8-10: 8 (20)	(Mean) 15.5	73 (41)	4 (10)	13 (32)	Not reported	Not reported	3 (8)

Sia (228)	Median: 69	T1:25(20) T2:57(45) T3:37(30) T4:6(5)	2-6: 40(32) 7: 60(48) 8-10: 25(20)	<10: 35(28) 10-20: 42(34) >20: 48(38)	120 (96)	Not reported	Not reported	Not reported	Not reported	Not reported
Aluwini (230)	Median: 70	T1:113(14) T2:263(34) T3:397(51) T4:9(1)	6: 238(30) 7: 355(45) 8: 115(15) 9: 67(9) 10: 7(1)	(Median) 14	519 (66)	Not reported	Not reported	> 50 cm^3 25% (HYPO), 25% (NFRT)	Not reported	75 (10)
Catton (233)	Median: 72	T1:636(53) T2:560(47) T3:0 T4:0	3+3: 113(9) 3+4: 762(63) 4+3: 331(28)	<5:219(18) 5-10:605(50) 10.1-20:382(32)	68(6)	Not reported	Not reported	Not reported	Not reported	Not reported

deCrevoisier (231)	Median: 70	T1:205(44) T2:112(24) T3:153(33) T4:0	4-6: 124(26) 7: 303(64) 8-10: 43(9)	(Median) 11	219 (47)	51	Not reported	Not reported	Not reported	Not reported
Wilson (232)	<75: 2725 =/>75: 491	T1:1170(37) T2:1756(56) T3:227(7) T4:0(0)	≤6:1122(35) 7: 1995(62) 8: 99(3)	(Mean) 11	3,126 (97)	342	Not reported	Median 37 (<75 years) / 42.7 (≥75 years)	Not reported	259 (8)

PSA, Prostate-specific antigen; ADT, Androgen deprivation therapy, DM; Diabetes mellitus; FU, Follow-up; HYPO, Hypofractionation; NFRT, Normofractionation

Table 3. Secondary Outcomes

Study	Haematuria, N(%)	Urinary Incontinence, N(%)	Urinary Retention, N(%)	120-month endpoint	Time to event	Predictive factors	Economic analysis
Al-Mamgani(229)	0(0)	2(6)	10(24)	No	No	No	No
Aluwini(230)	No	127(16)	No	No	No	Yes	No
Wilson(232)	No	No	No	No	Yes	No	No
deCrevoisier(231)	47(10)	65(14)	No	No	No	No	No
Sia(228)	1(1.25)	No	No	No	No	No	No
Catton(233)	No	No	No	No	No	No	No

Supplementary

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) 1946 to February 04, 2022

MEDLINE Search Strategy:

#	Searches	Results
1	exp Prostatic Neoplasms/	139475
2	(Prostat* adj2 (neoplasm* or cancer* or adenocarcinom* or mass or tumor)).tw,kf.	144866
3	or/1-2	177067
4	exp radiotherapy/ or exp brachytherapy/ or exp proton therapy/ or exp radiosurgery/ or exp radiotherapy, image-guided/ or exp x-ray therapy/	199125
5	(external beam radiotherap* or radiation therap* or radiotherap* or external beam* radiation therap* or EBRT).tw,kf.	265953
6	(brachytherapy* or curietherapy* or (radiotherap* adj3 implant*) or ((intracavit* or interstitial) adj3 radiotherap*) or ((radioisotope* or "radio isotope") adj3 therap*)).tw,kf.	20895
7	(SBRT or radiosurger* or (stereotactic adj3 bod adj3 radiotherap*) or (stereotactic adj3 bod adj3 radiation therap*)).tw,kf.	19006
8	(IMRT or (Intensity adj3 modulated adj3 radiotherap*) or (Intensity adj3 modulated adj3 radiation therap*) or (volumetric-modulated adj3 Arc adj3 Therap*) or	16734

	(Intensity-modulated adj3 arc adj3 therap*) or (volumetric modulated adj3 Arc adj3 Therap*) or (Intensity modulated adj3 arc adj3 therap*) or (helical adj3 tomotherap*)).tw,kf.	
9	(IGRT or ((image-guided or (image adj3 guided)) adj3 (radiotherap* or radiation therap*)) or (target organ adj3 (alignment or alinment) adj3 (radiotherap* or radiation therap*))).tw,kf.	3555
10	or/4-9	365075
11	Hematuria/ or haematuria.tw,kf.	15299
12	Radiation Injuries/ or radiation cystitis.tw,kf.	35207
13	bladder neck obstruction.tw,kf. or Urinary Bladder Neck Obstruction/	4743
14	urethral stricture.tw,kf. or Urethral Stricture/	6848
15	urinary retention.tw,kf. or Urinary Retention/	11837
16	urinary incontinence.tw,kf. or Urinary Incontinence/	38900
17	erectile dysfunction.tw,kf. or Erectile Dysfunction/	26275
18	or/11-17	133426
19	3 and 10 and 18	3154
20	human/	20150552
21	(human or male or men or man).mp.	12169833
22	20 or 21	22495199

23	19 and 22	3076
24	limit 23 to (english language and yr="2008 -2021")	1803
25	(letter or editorial or note or commentary).pt.	1763817
26	24 not 25	1738

Chapter 4: Genitourinary Toxicity After Pelvic Radiation: Prospective Review of Complex Urological Presentations

Rowan V. David, MBBS † ‡ ORCID 0000-0003-4483-1204

Asif Islam, MBBS † ORCID 0000-0002-6673-9348

John Miller, FRACS (Urol) † ORCID 0000-0001-8314-9107

Michael E. O'Callaghan, PhD † ‡

Arman A. Kahokehr, BHB, MBChB, PGDMSc, PhD, FRACS † ORCID 0000-0003-2618-3266

† Department of Urology, Lyell McEwin Hospital, Elizabeth Vale SA 5112

‡ College of Medicine and Public Health, Flinders University, Bedford Park South Australia.

Abstract

Introduction. Recent randomised controlled trials underestimate the incidence of genitourinary complications occurring more than five years following pelvic radiotherapy. This study aims to determine the burden of treatment at a single institution from late genitourinary complications after pelvic radiotherapy.

Materials and Methods. A prospective study of all presentations for genitourinary complications following pelvic radiotherapy at a tertiary urology department over 12 months was performed. Subgroup analysis was performed on patients with prostate cancer with late toxicity to compare patient demographics, radiotherapy, complication and management factors.

Results. There were 117 hospital encounters involving 46 patients with a 56% repeat encounter rate. Patients with prostate cancer were the predominant group (n= 39, 85%). External beam radiotherapy was the most common treatment modality (n= 41, 89%). The median (range) time from radiotherapy to encounter was seven years (0-23). Radiation-induced haemorrhagic cystitis was the most common presentation (n= 70, 60%). Fifty-two (44%) encounters for genitourinary toxicity were managed operatively and 37 (32%) involved a non-operative procedure. Nine patients required packed red cell transfusion, with a total of 154 units transfused. Patients with prostate cancer who presented with late genitourinary toxicity had higher median RTOG scores ($p = 0.037$), proportion of emergency admissions ($p = 0.048$) and frequency of clot urinary retention ($p < 0.001$).

Conclusion. There is a high burden of elective and emergency urology workload attributed to late pelvic radiation toxicity. Late genitourinary toxicity occurring ≥ five years after radiotherapy is common and often more severe.

Key words

Pelvic malignancy, Radiotherapy, Genitourinary toxicity, Hospitalisation, Secondary malignancy

Abstract Word Count: 242

Manuscript Word Count: 3872

Introduction

Radiotherapy is an important modality in the treatment of pelvic malignancy.(190, 242) However, long term complex genitourinary-toxicity can lead to radiation cystitis, ureteric and urethral strictures, necrotic bladder neck, urinary fistula, urinary incontinence and retention.(151-153) The real-life prevalence of patients presenting to hospital with late genitourinary toxicity occurring ≥ 5 years from radiotherapy may be under-researched because the complications often occur outside the follow-up period of controlled trials.(148-150, 193)

The significant burden of treatment in managing genitourinary toxicity after pelvic radiotherapy was highlighted in the recently published study by Ma et al., which demonstrated the range of complications requiring Urological admission.(188, 189) Our group has previously retrospectively shown that pelvic radiotherapy toxicity often occurs more than five years from treatment and results in a significant volume of hospital admissions and resource load on our real-world community tertiary hospital.(243)

This study primarily aims to prospectively determine the burden of treatment associated with late genitourinary complications occurring five years after pelvic radiotherapy at a tertiary community level institution. Secondary aims were to describe the patient characteristics and to compare the severity of toxicity amongst patients who underwent radiotherapy before and after five years from the date of captured presentation. The aim was not to find the *incidence* of late GU toxicity as this is not a population follow up level study.

Materials and methods

Patient Population

A prospective study of all patient encounters related to genitourinary toxicity following radiotherapy to a tertiary urology department between November 2018 and November 2019 was performed. A hospital encounter was defined as any patient presentation to the outpatient clinic, emergency department, operating theatre, or ward associated with complications of pelvic radiotherapy toxicity. Hospital encounters that were suspected to be related to radiation-induced toxicity were prospectively recorded and the association was retrospectively confirmed based on the results of further investigations. Encounters that were non-urological or not cystoscopically confirmed to be radiotherapy-related were excluded.

Ethical approval

Ethical approval was granted by the Northern Adelaide Clinical Human Research Ethics Committee (EC00188), as it met the requirements of the National Statement on Ethical Conduct in Human Research (2007, updated 2018) and the Northern Adelaide Local Health Network Research Governance policy.

Data Collection

Patients were identified by urology staff including Consultants, Registrars, Junior medical staff and Nurse consultants**.** Patient demographic data, including Charlson comorbidity score, primary malignancy and use of antiplatelet or anticoagulant medications, were collected. In cases of prostate cancer, ISUP grade, clinical stage, and Prostate-specific antigen (PSA) at diagnosis were recorded. The

radiotherapy modality, treatment intent, total dose in Gray (Gy) and number of fractions were included. The time from treatment to presentation, type of admission (elective or emergency), complication type, number of bed days and type of hospital management required were recorded. The year of radiotherapy treatment was categorised as occurring either before or from 2010 onwards, as a surrogate indicator of outdated and more contemporary radiotherapy techniques, respectively, because there was a transition from Three-Dimensional Conformal EBRT towards IMRT in South Australia during this period.

Management data was divided into non-surgical, minor operative procedures and major operative procedures. Non-surgical procedures included the use of urethral indwelling catheters, continuous bladder irrigation and trial of void. Minor operative procedures included flexible cystoscopy, urethral dilations, nephrostomy exchanges, ureteric stent procedures, rigid cystoscopy and cystoscopic bladder washout. Major operative procedures included transurethral bladder tumour resection (TURBT) and any open or laparoscopic surgery.

Complication Classification

Complications were divided into categories (radiation-induced haemorrhagic cystitis, stricture, fistula, urinary incontinence, necrotic bladder neck contracture, and radiation-associated secondary malignancy [RASM]). All encounters for radiation-induced haemorrhagic cystitis, fistula, stricture and necrotic bladder neck contractures were cystoscopically confirmed. We recorded the presence of pre-treatment urothelial carcinoma, urethral stricture disease or bladder neck contracture, as well as prior urological instrumentation or trauma. RASM was defined as histologically confirmed secondary pelvic malignancy occurring within the radiation field at least five years following pelvic radiotherapy.(244, 245) Complications were graded according to the Radiotherapy Oncology Group (RTOG) scoring system.(246)

Statistical Analysis

Categorical variables were compared using the Fischer Exact Test. Continuous variables were compared using the One-way ANOVA or the Kruskal-Wallis Rank Sum test for parametric and non-parametric data, respectively. Statistical significance was set at $p < 0.05$.

Results

Patient Demographics and Clinical Data

Table 1 summarises the patient demographic, clinical and radiotherapy dosimetry characteristics of the included patients. Of the 39 patients with prostate cancer, most underwent curative intent radiotherapy (n=27, 69%), followed by non-curative intent radiotherapy (n=7, 18%), and there were 5 (13%) patients who had no available treatment intent data. Patients with prostate cancer who underwent non-curative radiotherapy had a significantly greater proportion of elective admissions (76 vs 51%, p = 0.041) and outpatient department encounters (48 vs 18%, p=0.041). Of the five patients with missing treatment intent data, most had cystoscopically confirmed radiation-induced haemorrhagic cystitis (n = 4, 80%). The remaining patient had a urethral stricture in the absence of prior radical prostatectomy or transurethral resection of prostate.

External beam radiotherapy was the main type of radiotherapy used for patients with prostate cancer (n=34, 87% Of the 34 patients presenting with radiation-induced haemorrhagic cystitis, 32 (94%) were on a form of anticoagulation or antiplatelet therapy (Table 2). However, subgroup analysis performed on the 30 patients with prostate cancer revealed no statistically significant differences in the presence of antiplatelet ($p > 0.05$) or anticoagulant ($p > 0.05$) medication use amongst patients presenting with or without haematuria. Furthermore, there were no significant differences in the rate of admission, readmission or RTOG grade amongst patients with haematuria regardless of anticoagulant or antiplatelet use.

Encounter Data

There were 46 patients and 117 hospital encounters included in the study (Table 1). Of the 117 hospital encounters, most occurred in the elective setting (n= 60, 54%). There were 66 (59%) repeat

encounters, including 28 (24%) unplanned and 34 (29%) repeat encounters occurring within one month of the previous encounter, respectively. There were 52 admissions for genitourinary toxicity, which accounted for 3% of the total 1524 urological admissions at our tertiary centre over the study period. Of the 52 admissions, 23 (44%) were readmissions, and 15 (29%) were unplanned. There were 22 patients with at least one emergency admission related to radiotherapy-induced toxicity, with a total of 38 emergency admissions. These 38 emergency admissions accounted for 7% (38/558) of the overall emergency admissions to our Urology unit over the study period. There were 37% (14/38) unplanned emergency readmissions. Furthermore, there were 14 emergency operative procedures performed for patients with radiotherapy-related toxicity. These 14 emergency operative procedures accounted for 4% (14/364) of the overall emergency operative procedures performed by our Urology unit over the study period. The total length of stay for patients admitted with pelvic radiotherapy-related toxicity was 405 days. The total length of stay due to this pelvic radiotherapy-related toxicity accounted for 16% (405/2500) of the total length of stay for all patients admitted at our centre during the study period.

Radiotherapy Complication Type and Management

The median RTOG toxicity score was three, indicating mostly moderate-severe toxicity (Figure 1). Cystoscopically confirmed radiation-induced haemorrhagic cystitis was the most common complication and accounted for 70 (60%) of overall encounters, including 33 (28%) encounters for clot retention (Figure 2). Urinary tract stricture disease was the second most common toxicity (18/117, 15% encounters) and affected four patients (n=3 urethral, n=1 ureteral). (Figure 2) The patients with urinary tract stricture disease, as well as the two patients with necrotic bladder neck contracture, were all treated with primary EBRT in the absence of pre-existing known urethral stricture disease, urological

instrumentation or urological trauma. Three patients (7%) were diagnosed with urothelial carcinoma of the bladder ≥ 5 years following radiotherapy. (Table 3)

The median (range) time from prostate cancer radiotherapy treatment to presentation was 8 (0-23) years. Subgroup analysis was performed to compare patients with prostate cancer who presented with genitourinary toxicity < five and ≥ five years from the time of pelvic radiotherapy. Patients who presented with genitourinary toxicity ≥ five years following radiotherapy had a higher median [range] RTOG grade (4 [3-4] vs 3 [2-4]), p = 0.037. They also had a greater proportion of emergency admissions (37/69 = 54% vs 10/31 = 32%, p = 0.048), and clot retention (28/69 (41%) vs 2/31 (6.5%), p < 0.001). (Table 4)

Management

Of the 117 hospital encounters, 85 (73%) required a urological intervention, with 35 (30%) non-operative and 50 (43%) operative procedures**.** The most common non-operative, minor and major operative procedures were continuous bladder irrigation (n = 27 encounters, 23%), flexible cystoscopy (n= 21 encounters, 18%) and Transurethral Resection of Bladder Tumour (TURBT) (n= 3 encounters, 3%) respectively.

There was one laparoscopic-assisted defunctioning colostomy, which was performed on a patient who developed a T4 radiation-associated secondary urothelial malignancy of the bladder with a recto-urethral fistula. Nine patients required packed red blood cell transfusions, with a median of three transfusions (range 1-130) and a total of 154 packed red cells given. Table 4 summarises the urological encounters, pelvic toxicity, and management required.

Discussion

Late radiation-induced genitourinary toxicity occurring ≥ five years following treatment is not an uncommon presentation to our unit. Patients with prostate cancer who presented with late genitourinary sequelae ≥ five years after radiotherapy were associated with greater median RTOG grade toxicity ($p = 0.037$) as well as more frequent emergency admissions ($p = 0.048$) and radiation-induced haemorrhagic cystitis with urinary clot retention ($p < 0.001$). (Table 4) Furthermore, these patients with late genitourinary toxicity contributed to an already complex burden of treatment on our tertiary community centre Urology department. These treatment-related complications frequently required intervention, with 85 (73%) of encounters requiring a form of urological intervention and 50 (43%) requiring operative management. Furthermore, there was a significant volume of repeat encounters (59%), particularly unplanned emergency encounters (24%).

The most common presentation was cystoscopically confirmed radiation-induced haemorrhagic cystitis. Of the 30 patients with prostate cancer who presented with radiation-induced haemorrhagic cystitis, 14 (47%) patients were on an antiplatelet, and 10 (33%) patients were on anticoagulation therapy. However, there were no statistically significant differences amongst patients who presented with or without haematuria regarding the presence of antiplatelet ($p > 0.05$) or anticoagulant ($p > 0.05$) use. Furthermore, there were no significant differences in the rate of admission, readmission or RTOG grade amongst patients with haematuria with or without a history of anticoagulant or antiplatelet use. None were admitted to our centre with haematuria prior to the completion of prostate EBRT. Therefore, we were able to retrospectively conclude that these patients admitted with haematuria had radiation-related toxicity. Furthermore, it appears reasonable to include these patients with haematuria and antiplatelet or anticoagulant medication in the evaluation of the burden of treatment

because they did not account for a disproportionately large proportion of admissions or severe RTOG-grade complications.

Similar admission volumes have been demonstrated in the retrospective study by Handmer et al., which identified that radiotherapy-related complications accounted for 3.7% of the 1748 total urology admissions in 1 year.(247) Our study provides prospective confirmation of this high proportion and reports that radiotherapy-related complications accounted for 3% of the total 1524 urological admissions over the one-year study period. Similar operative rates have been demonstrated in the literature, with Ma et al. reporting a 67% operative rate in their study.(188, 248) Most genitourinary toxicity events occurred outside the typical follow-up endpoints reported by most multi-institutional cohort studies and randomised control trials. Furthermore, three (7%) patients included in this study had a secondary primary bladder malignancy diagnosed ≥ 5 years following pelvic radiotherapy. (Table 3) However, the current study is unable to determine the incidence of RASM. The recent study by Mazzone et al. reported a 6% 20-year incidence of RASM following brachytherapy (249) which is significantly higher than those typically reported in the literature.(169) A population-level retrospective study by Moschini et al. of the Surveillance, Epidemiology and End Results-Medicare database included 84,397 men with localised prostate cancer treated with EBRT or RP from 1988 to 2009 and found 5- and 10-year cumulative incidence of primary bladder cancer of 1.26% and 2.34% in the EBRT cohort.(250) Further prospective evaluation of the incidence of secondary pelvic malignancy following radiotherapy is needed at a population level.

Despite technological improvements in prostate EBRT delivery, there has not been a consistent reduction in treatment-related late genitourinary (GU) toxicity demonstrated over the last decade. (114-116) In our study, there were 32 patients with prostate cancer treated with EBRT (n= 13 < 2010, n = 19 ≥ 2010). Those treated ≥ 2010 mostly had IMRT (n=9/12, 75%) followed by VMAT (n=3/12, 25%).

Whilst patients treated < 2010 mostly had unknown treatment options (n=11/19, 58%), these patients would have received outdated and less-conformational RT techniques than patients treated after 2010. There was no difference in median (IQR) RTOG (4 [3, 4] vs 3 [3, 4], p = 0.90) or length of stay (4 [2, 4] vs 4 [3, 7], p =0.30) between patients treated before and after 2010. Furthermore, there were no differences in the proportion of patients with hospital admission (7 / 13 [54%] vs 13 / 19 [68%], p=0.47), hospital representation (1 / 13 [8%] vs 1 / 19 [5%], p >0.99), readmission (1 / 13 [8%] vs 0 / 19 [0%], p = 0.41), emergency admissions (8 / 13 [62%] vs 10 / 19 [53%], p= 0.62).

This study has several limitations. Most (59%) of patients had unknown radiotherapy treatment regimes, and many would have had now outdated treatments such as three-dimensional conformal radiotherapy. Of the 46 included patients, there were 13 patients treated with radiotherapy before 2010, 11 patients treated from 2010 onwards and 4 patients with missing treatment date data. In the subgroup analysis of (n=32) patients with prostate cancer treated by EBRT, there were 28 patients with missing technique data. Of these 28 patients, more were treated before 2010 than from 2010 onwards (n=11 vs n=7). The current study is unable to determine the incidence of genitourinary toxicity or RASM after radiotherapy due to the sample framework used. Instead, this study provides a one-year snapshot of the burden of treatment associated with radiotherapy toxicity at a single institution and highlights the proportion of patients with toxicity occurring >5 years from the treatment date. Further population-level studies with long-term follow-up of > five years are required to determine the cumulative incidence of treatment-related toxicity and predictors of toxicity, including the year of treatment. These studies should select patients treated by a specific radiotherapy delivery technique, field and treatment intent. Patients should be determined to be at risk from the date of radiotherapy treatment onwards. The current study fails to capture genitourinary toxicity-related encounters at community health centres such as specialist nursing clinics, allied health services, radiology providers

and general practitioners in our population catchment area. The patients may have had admissions and treatment for their pelvic toxicity at other tertiary centres, which have not been included in the current study. Future studies should also determine the impact on patient's quality of life and the associated cost burden with genitourinary toxicity following pelvic radiotherapy.

Conclusion

In this prospective study of patients presenting to a single tertiary-level hospital, there is a significant proportion of patients with late genitourinary toxicity occurring ≥ five years after radiotherapy. There is a high burden of elective and emergency urology workload attributed to delayed pelvic radiation toxicity. The number of patients with RASM in this study (secondary bladder malignancy was detected in 7% of patients) following pelvic radiotherapy requires further research and assessment. Delayed genitourinary toxicity following radiotherapy may result in particularly complex urological presentations and burden of care in the long term.

Main Points

- There is a significant volume of hospital encounters due to radiation toxicity resulting in elective and emergency urological admissions at our real-world tertiary level hospital.
- The majority of the genitourinary toxicity events occurred outside of the typical follow-up endpoints reported by most multi-institutional cohort studies and randomised control trials
- Delayed genitourinary toxicity occurring ≥ 5 years following radiotherapy may result in particularly severe toxicity and burden of care in the long term.
- The number of patients with RASM in this study (secondary bladder malignancy was detected in 7% of patients) following pelvic radiotherapy requires further research and assessment.

Chapter 5: Incidence Of Genitourinary Complications Following Radiation Therapy For Localised Prostate Cancer

Rowan V. David, MBBS ‡ † ORCID 0000-0003-4483-1204

Arman A. Kahokehr, PhD, FRACS ‡ ^ ORCID 0000-0003-2618-3266

Jason Lee, MS, FRACS (Urol) ‡ †

David I. Watson, PhD, FRACS ‡ ORCID 0000-0002-7683-2693

John Leung, PhD, FRANZCR ¥ ǂ ORCID 0000-0003-1834-9131

Michael E. O'Callaghan, PhD ‡ † ¶^ ORCID 0000-0001-5038-5859

ǂ College of Medicine and Public Health, Flinders University, Bedford Park South Australia.

† Department of Urology, Flinders Medical Centre, SA Health, Australia.

¥ GenesisCare, Adelaide, Australia

¶ South Australian Prostate Cancer Clinical Outcomes Collaborative

^ University of Adelaide, Discipline of Medicine, Freemasons Foundation Centre for Men's Health

Abstract

Purpose. Studies of genitourinary toxicity following radiotherapy for prostate cancer are mainly from high volume single institutions and the incidence and burden of treatment remain uncertain. Hence we determine the cumulative incidence of treatment-related genitourinary toxicity in patients with localised prostate cancer treated with primary external beam radiotherapy (EBRT) at a state population level.

Methods. We analysed data from a prospective population-based cohort, including hospital admission and cancer registry data, for men with localised prostate cancer who underwent primary EBRT without nodal irradiation between 1998 and 2019 in South Australia. The 10-year cumulative incidence of genitourinary toxicity requiring hospitalisation or procedures was determined. Clinical predictors of toxicity and the volume of admissions, non-operative, minor operative and major operative procedures were determined.

Results. All the included patients (n= 3,350) had EBRT, with a median (IQR) of 74Gy (70-78) in 37 fractions (35-39). The 10-year cumulative incidence of was 28.4% (95% CI 26.3 – 30.6) with a total of 2,545 hospital admissions, including 1,040 (41%) emergency and 1,893 (74%) readmissions. The 10-year cumulative incidence of patients in this cohort requiring a urological operative procedure was 18% (95% CI 16.1 – 19.9), with a total of 106 (4.2%) non-operative, 1,044 (41%) minor operative and 57 (2.2%) major operative urological procedures.

Conclusion. Genitourinary toxicity after radiotherapy for prostate cancer is common. Although there continue to be advancements in radiotherapy techniques, patients and physicians should be aware of the risk of late toxicity when considering EBRT.

Keywords: “prostate cancer”, “radiotherapy”, “radiation therapy”, “external beam radiotherapy”, “genitourinary complications”, “urethral stricture”, “radiation cystitis”

Abstract Word Count: 239

Manuscript Word Count: 2915

Introduction

Prostate cancer is the second most common form of cancer affecting men worldwide.(10) The majority (94%) of patients with prostate cancer have curable localised disease, for which the treatment options include active surveillance, surgery or radiotherapy.(17) Radiotherapy is a common treatment for localised prostate cancer.(92, 93) However, the incidence of late genitourinary toxicity (GUT) and its associated burden of treatment across a variety of practice settings remains poorly understood. Radiotherapy injuries often present late due to progressive fibrosis and the difficulties in accurately recording these long-term adverse effects are reported in the literature frequently.(139, 187, 251) The majority of studies on the incidence of genitourinary toxicity after radiotherapy and its associated burden of treatment are studies from specialised high-volume single centres.(188, 251, 252) There are few multi-institutional studies (114, 253, 254) and the randomised trials often involve a disproportionately younger and healthier patient demographic when compared to a typical population.(255, 256) An improved understanding of the incidence of late treatment-related genitourinary toxicity following prostate radiotherapy would enhance patient-centred decision making.(187)

The primary aim of this study was to determine the cumulative incidence of treatment-related genitourinary toxicity following external beam prostatic radiotherapy in patients with localised prostate cancer at a population level. The secondary aims were to determine clinical factors predictive of genitourinary toxicity and the volume of admissions and procedures required.

Material and Methods

Participants

A population-based prospective cohort study of all patients with localised (T1- T3, according to the American Joint Committee on Cancer) biopsy-proven prostate cancer who underwent primary external beam radiotherapy (EBRT) was performed between January 1, 1998, and January 31, 2019, in South Australia. We excluded patients with metastatic prostate cancer and those without a histological tissue diagnosis of prostate cancer. We excluded patients who underwent adjuvant radiotherapy following either radical prostatectomy, or prior radiotherapy treatment (Figure 1).

The South Australian Prostate Cancer Clinical Outcome Collaborative (SA-PCOCC) registry prospectively recruits >90% of patients who are diagnosed with prostate cancer in South Australia. We linked patient records from the SA-PCCOC registry with the Integrated South Australian Activity Collection (ISAAC) Hospital Administrative Database to identify patients who presented to any major hospital in South Australia with treatment-related genitourinary toxicity, as defined by a pre-selected list of International Classification Disease 10th Edition (ICD-10-AM)/ Australian Classification of Health Interventions (ACHI). Data linkage was performed by matching patient identifiers within Envido (Adelaide, South Australia). The list of admission and procedures codes were selected based on the literature,(187) and recommendations from a multidisciplinary panel, including a urologist, radiation oncologist, general surgeon and a clinical epidemiologist.(Appendix 1) Baseline characteristics including age, Charlson Comorbidity Index, anticoagulant medication use, and oncological characteristics, including T-stage, ISUP grade and baseline Prostate-specific antigen (PSA) level were extracted. Treatment-related factors including dose (Gray), fractionation and date of treatment completion were also extracted.

Primary Outcomes

The treatment-related complication categories used were hospital admission and urological procedures associated with genitourinary toxicity. Genitourinary toxicity-related hospital admission or procedures required for each patient were identified using the ISAAC Database (using the relevant hospital admission or procedure code based on the ICD-10 or ACHI codes). The time to the first genitourinary toxicity-related hospital admission, death or censor were analysed to determine the cumulative incidence of genitourinary toxicity. Patients were censored at the last date of the last admission in the ISAAC electronic hospital database.

Secondary Outcomes

Demographic factors assessed included age (continuum), Charlson comorbidity score, diabetes (yes/ no), hypertension (yes/ no), use of anticoagulant (yes/ no), smoking history (yes/ no), bladder outlet obstruction (yes/ no), Transurethral resection of the prostate (TURP) before radiotherapy (yes/ no), T stage (T1 vs T2 vs T3), initial prostate-specific antigen level (continuum) and dose (continuum and > 80Gy vs ≤ 80Gy). Furthermore, the admission data was separated into patients who received EBRT <2009 and ≥ 2009, to account for the use of Three-dimensional conformal radiation therapy (3DCRT) and Intensity Modulated Radiotherapy/ Volumetric modulated arc therapy (IMRT/VMAT), respectively.

The overall burden of treatment, as defined by the volume of admissions as well as non-operative, minor operative and major operative procedures was determined. Non-operative procedures were defined as ACHI codes involving urethral catheterization or bladder irrigation. Minor operative procedures were defined as ACHI codes involving urethral dilation, cystoscopy, suprapubic catheter insertion, retrograde pyelogram, antegrade or retrograde ureteric stenting. Major operative

procedures were defined as ACHI codes involving transurethral resection, ureteroscopy or open surgical procedure.

The outcomes were reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.(257)

Statistical Analysis

The cumulative incidence of hospitalisation for treatment-related genitourinary complications was determined. Patients were considered to be at risk of complications from the end date of their radiotherapy until either the date of their first admission related to genitourinary toxicity, last date of follow-up or date of death, according to the SA-PCCOC registry. The patient-related baseline characteristics and the volume of hospital admissions and procedures were summarised and compared. Categorical variables were compared using the Fischer Exact Test or Pearson's chi-square test. Continuous parametric and non-parametric variables were compared using one-way ANOVA or the Kruskal-Wallis Rank Sum test, respectively. P-values were calculated for each variable compared and $P < 0.05$ was considered significant. Relationships between genitourinary toxicity-related hospital admission and patient, tumour or treatment characteristics were analysed using Cox proportional hazard regression at univariate and multivariate levels. The regression analyses' results are presented as a hazard with a 95% confidence interval. Missing clinical data was replaced using multiple imputations by chained equations before regression analysis. (Figure 1) All statistical analysis was performed using R language, Version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria).(258)

Results

There were 3,350 patients with prostate cancer treated with primary external beam radiotherapy in this cohort. We excluded 820 patients who were initially treated surgically, with either robotic-assisted laparoscopic prostatectomy (n=579) or open radical prostatectomy (n= 241). We also excluded 388 patients who were treated with brachytherapy before external beam radiotherapy and four patients with T4 disease (Figure 1). All the included patients underwent primary EBRT, with a median (IQR) of 74Gy (70-78) in 37 fractions (35-39). The median (IQR) age at diagnosis of the included patients was 71 (66-76). Most patients had Stage II (n= 914, 58%) and high-risk disease (n=1,517 [51%]), according to the National Comprehensive Cancer Network (NCCN) 2017 scoring system. Table 1 summarises the patient demographic, oncological and treatment dosimetric characteristics.

The 5 and 10-year cumulative incidence of admission to hospital for treatment-related genitourinary toxicity were 14.8% (95% CI 13.4-16.2) and 28.4% (95% CI 26.3 – 30.6), respectively (Figure 2). The 5 and 10-year cumulative incidence of patients in this cohort requiring a urological operative procedure for a treatment-related GUT were 9.9% (95% CI 8.7 – 11) and 18% (95% CI 16.1 – 19.9), respectively (Figure 2). The five-year cumulative incidence of treatment-related genitourinary toxicity hospital admission were 18 % (95% CI 15 – 20%) and 12% (95 CI 11-14), amongst patients treated before and after 2010, respectively ($p < 0.001$; Figure 3).

There were 652 (19.5%) prostate cancer patients who required hospital admission for genitourinary toxicity after primary EBRT, with a total of 2,545 hospital admissions, of which 1,040 (41%) occurred in the emergency setting. Four-hundred and nine (63%) of these patients had multiple admissions, with a total of 1,893 (74%) readmission related to genitourinary toxicity. Haematuria was the most common

genitourinary toxicity (n= 386, 59%), and of these patients, 108 (28%) required blood product transfusion, 8 (2%) required HBOT and 4 (1%) required surgical urinary diversion. Table 2 summarises the treatment-related outcomes amongst patients with genitourinary toxicity following primary EBRT. Four-hundred and nine (12%) patients developed genitourinary toxicity which required management with a urological procedure, with a total of 106 (4.2%) non-operative, 1,044 (41%) minor and 57 (2.2%) major operative urological procedures (Table 3). The most common procedure was diagnostic cystoscopy (701/1101 [64%] of all procedures).

Patients with BOO without TURP prior to EBRT, had the highest 10-cumulative incidence of admission for genitourinary toxicity (77% [70%, 82%] vs 20% [18%, 22%] p <0.001; Table 3, Figure 3). In addition, patients with BOO without TURP prior to EBRT had the most hospital admissions (178/246 [72%] vs 474/3104 [15%], p < 0.001), emergency admissions (136/246 [55%] vs 273/3104 [8.8%], p < 0.001) and readmissions (110/246 [45%] vs 282/3104 [9.1], p < 0.001), for treatment-related genitourinary toxicity (Table 1). Patients with BOO without TURP before EBRT were at the highest risk of developing genitourinary toxicity after adjustment for age, diabetes, smoking, urinary incontinence and EBRT before 2009 (HR 5.87 [95% CI 4.8-7.17], p < 0.001; Table 4).

Discussion

This is one of few studies to evaluate the cumulative incidence of treatment-related genitourinary complications following radiotherapy for prostate cancer at a population level and the first in Australia. The high 10-year cumulative incidence (28.4%) of hospital admission due to treatment-related genitourinary toxicity exceeds previous estimates following primary EBRT.(93, 187, 251) The date of radiotherapy made a minimal difference in the 10-year cumulative incidence of genitourinary toxicity-related admission amongst patients in this cohort, and was not an independent predictor of genitourinary toxicity after adjustment for age, comorbidity, smoking and BOO in multivariable analysis (HR 0.87 [95% CI 0.72, 1.04), p=0.12; Table 4). This is also the first Australian study to determine the volume of admissions and urological procedures for the management of radiotherapy treatment-related genitourinary complications at a population level. Greater than one-third of genitourinary toxicity-related hospital admissions occurred in the emergency setting. There were a significant number of admissions with a prolonged length of stay of ≥ 3 days. Whilst haematuria was the most common presentation, we are unable to confirm the diagnosis of radiation cystitis due to the limitations associated with administrative coding, we can infer the diagnosis of severe hemorrhagic radiation-induced cystitis occurred in 12/3,351 (0.4%) of patients, with 8/3,351 (0.2%) and 4/3,351 (0.1%) patients requiring HBOT and surgical urinary diversion, respectively. A significant number of patients (18%) required an invasive urological procedure. There were significantly fewer hospital admissions and procedures amongst patients treated with EBRT after 2009, which may reflect improvements in radiotherapy techniques or the shorter follow-up in this group, which likely underestimated late toxicity.

Three large population-based studies have been published in this area with patients from the USA,(242) Canada,[6] and England.(251) A total of 307,252 patients were described. (93, 187, 251)

However, like several other studies,(193, 259) these studies did not include patient baseline oncological characteristics,(187) or important treatment-related factors, including the dose and fractionation use in the radiation treatment used.(187, 242, 251) The study by Sheets et al., was the first study to demonstrate an increased risk of patients developing genitourinary toxicity following IMRT as compared to conformal radiation therapy, (absolute risk, 5.9 vs 503 per 100 person-years; relative risk, 1.12; 95% CI, 1.03-1.20).(242) Only one of these studies reported 5- year cumulative incidence of treatment-related genitourinary toxicity, which was determined to be 10.7 (95% CI 10.1-11.3).(251) The estimate determined by the latter study was limited by missing values for the prostate cancer risk group (n=5753) and radiotherapy treatment region (n= 3793).(251) The other study reported a 22.2% (95% CI 21.7-22.7) 5-year cumulative incidence of admission for either genitourinary or gastrointestinal treatment-related complication and a 32.0% (95% CI 31.4-32.5) 5-year cumulative incidence of needing a urological procedure.(187) All three studies lacked a 60-month endpoint and this may have led to an underestimation of the late genitourinary toxicity events, as is the case with many other studies.(193, 260) The majority of studies of > 5-year genitourinary toxicity are not population-based, tend to focus on a narrower range of toxicity and have a shorter follow-up duration.(188, 261)

Patients with bladder outlet obstruction without TURP before EBRT were at the highest risk of developing genitourinary toxicity after adjustment for age, diabetes, smoking, urinary incontinence and EBRT before 2009 (HR 5.87 [95% CI 4.8-7.17], $p < 0.001$; Table 4). Similarly, many other studies have also shown that pre-existing urinary symptoms can influence radiotherapy-related genitourinary toxicity.(194, 210, 262) TURP before radiotherapy demonstrated a protective effect against genitourinary toxicity amongst patients with bladder outlet obstruction in our study (HR 3.6, 95% CI, 3.01-4.46, $p < 0.001$), however other studies have shown TURP might deteriorate late urinary symptoms.(211, 263) Similarly, several other studies (194, 206, 262) have supported our finding that

diabetes is an independent predictor of genitourinary toxicity in patients with prostate cancer treated with radiotherapy (HR 1.25, 95% CI, 1.08-1.53, p < 0.004). Furthermore, the role of diabetes may be increasingly important in the era of dose-escalated (≥ 74Gy) IMRT, as shown by Kalakota et al., who reported diabetes to be an independent predictor of late grade 3 genitourinary toxicity (RR 2.74, p = 0.004) in their multivariate analysis.(264) However, a few studies did not support the impact of diabetes on treatment-related genitourinary toxicity.(121, 205, 265)

Less known is the impact of age on radiation-induced genitourinary toxicity, which may reflect physiological changes and altered clinical decision-making. Whilst we found that increased age was associated with significant lower cumulative 5,10- and 15-year EFS rates (p = 0.041, Table 4) in univariate analysis (HR 1.02 95% CI 1.01-1.03, p < 0.001), this did not retain significance in multivariable regression (p = 0.6). However, other studies have shown increased age to be an independent predictor of treatment-related genitourinary toxicity (182, 187, 194), including the study by Nam et al., which reported a higher incidence of hospital admission due to genitourinary toxicity (HR 1.007, 95% CI 1.003-1.010, p <0.0001) amongst patients with prostate cancer treated with radiotherapy (n = 16,595) in a multivariable analysis performed in Cox proportional hazard modelling, adjusted for age and comorbidity treatment.(187)

Similarly, whilst we found an increased risk of genitourinary toxicity amongst patients with a history of anticoagulation medication use on univariable analysis (HR 2.03 95% CI 1.67-2.49, p < 0.001), the significance was not retained in multivariable analysis (p = 0.3). However, in multivariable analysis, other studies have shown an increased risk of haematuria associated with anticoagulant use (RR 2.89, p=0.01).(194)

Whilst we found that Charlson comorbidity score was not associated with genitourinary toxicity, in univariate analysis (HR 1.06, 95% CI 0.99-1.12, p < 0.091), the study by Nam et al. found that increased comorbidity, as measured by the Johns Hopkins University ACD Case-Mix System, was associated with

a higher incidence of hospital admission in multivariate analysis (HR 1·08, 95% CI 1·07–1·09, p<0·0001).(187)

Similarly, whilst we found no statistically increased risk of toxicity for patients with a history of hypertension (HR 3.91, 95% CI 0.98-15.7, p = 0.12) on univariable analysis, other studies have shown a positive association (205, 266). Contrastingly, other studies have reported a protective effect of hypertension, suggested to be associated with antihypertensive medication intake (267), with Barnett et al. reporting a correlation with decreased risk of a poor urinary stream (HR 0.25, 95% CI 0.09-0.71, p=0.009).(205)

Similarly, the data on dose-related genitourinary dysfunction has been controversial, and whilst some studies suggested a correlation between dose to the bladder and genitourinary toxicity (194, 196, 262, 268-273), this has generally been unconfirmed by other authors (211), including the current study in univariable regression analysis (p= 0.4). This inconsistency may be due to confounding differences in treatment scheme (target volume, position during treatment, bladder volume variation, technique, dose), patient characteristics, grading scale and the length of follow-up.(274-276)

Similarly, patients who received radiotherapy before 2009 had a higher 10-year cumulative incidence of admission for genitourinary toxicity (29% [26%, 31%] vs 19% [16%, 21%], p <0.001; Table 3, Figure 3). In addition, patients with EBRT before 2009 had more hospital readmissions for genitourinary toxicity (1,879 [74%] vs 1,354 [77%], p <0.001), urinary retention (757 [43%] vs 287 [38%], p = 0.032) as well as more non-operative (p<0.001) and minor-operative procedures (p<0.001) compared with patients who received radiotherapy ≥ 2009 (Table 1). However, date of treatment before 2009 was not an independent predictor of hospitalisation for genitourinary toxicity, after adjustment for age, comorbidity, smoking and BOO (HR 0.87 [95% CI 0.72, 1.04), p=0.12; Table 4).

Our study has several limitations. Firstly, whilst the use of administrative data coding based on diagnostic and admission codes has been validated in other claims-based studies assessing severe pelvic adverse effects after radiotherapy,(277) the number of genitourinary complications has likely been under-reported given the retrospective data-linkage methods used. For example, we would not have captured complications that are non-life-threatening (e.g. lower urinary tract symptoms from urethral stricture or bladder neck contracture) or which do not require further procedures. Furthermore, the sampling methodology used does not account for patients who may have had complications in other states. However, the study benefits from population-level data and longer duration of follow-up. In addition, we are unable to establish a causal link between radiation treatment and the reason for admission. These potential confounding factors may lead to the incorrect attribution of radiation-related toxicity in our dataset, especially for late complications given the distant temporal relationship.(193, 278) The work presented here is descriptive and may motivate further investigations focusing on causal pathways, mechanisms of action and preventive strategies. Toxicity grades were unable to be reported, as these were not coded in administrative data. The study does not include radiation-associated secondary malignancy, gastrointestinal or other pelvic treatment-related complications (e.g. rectal and pubic symphysis fistula).

Conclusion

Genitourinary complications after radiotherapy for prostate cancer are common. Although there continue to be significant advancements in radiotherapy techniques, patients and physicians should be aware of the risk of late toxicity when considering treatment options for prostate cancer. Further research is needed to identify predictive factors and develop models predicting late treatment-related genitourinary toxicity to improve pre-treatment counselling and enhance patient-centred decision making.

Author Declarations

Competing Interests

The authors have no competing interests to declare that are relevant to the content of this article.

Ethics Approval

The SA-PCCOC database has been approved by the Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC). Approval to access the database was granted by the SA-PCCOC steering committee. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Author Contributions

RV David: project development, data collection, data analysis and manuscript writing.

AA Kahokehr: data analysis and manuscript editing.

J Lee: project development and manuscript editing.

J Leung: data analysis and manuscript editing.

DI Watson: project development and manuscript editing.

ME O'Callaghan: project development, data analysis and manuscript editing.

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Chapter 6: Predicting Post-radiation Genitourinary Hospital Admissions In Patients With Localised Prostate Cancer

Rowan David, MBBS ‡ † ORCID 0000-0003-4483-1204

Mrunal Hiwase, MBBS ‡

Arman A. Kahokehr, BHB, MBChB, PGDMSc, PhD, FRACS ‡ ^ ORCID 0000-0003-2618-3266

Jason Lee, MS, FRACS (Urol) ‡ †

David I. Watson, PhD, FRACS ‡ ORCID 0000-0002-7683-2693

John Leung, PhD, FRANZCR ¥ ǂ ORCID 0000-0003-1834-9131

Michael E. O'Callaghan, PhD †‡ ¶^ ORCID 0000-0001-5038-5859

‡ College of Medicine and Public Health, Flinders University, Bedford Park, South Australia.

† Department of Urology, Flinders Medical Centre, SA Health, Australia.

¥ GenesisCare, Adelaide, Australia

¶ South Australian Prostate Cancer Clinical Outcomes Collaborative

^ University of Adelaide, Discipline of Medicine, Freemasons Foundation Centre for Men's Health

Abstract

Purpose. The risk of treatment-related toxicity is important for patients with localised prostate cancer to consider when deciding between treatment options. We developed a model to predict hospitalisation for radiation-induced genitourinary toxicity based on patient characteristics.

Methods. The prospective South Australian Prostate Cancer Clinical Outcomes registry was used to identify men with localised prostate cancer who underwent curative intent external beam radiotherapy (EBRT) between 1998 and 2019. Multivariable Cox proportional regression was performed. Model discrimination, calibration, internal validation, and utility were assessed using C-statistics and Area Under ROC, calibration plots, bootstrapping, and decision curve analysis, respectively.

Results. There were 3,243 patients treated with EBRT included, of which 644 (20%) patients had a treatment-related admission. In multivariable analysis, diabetes (HR 1.35, 95% CI 1.13-1.60, $p < 0.001$), smoking (HR 1.78, 95% CI 1.40 – 2.12, $p < 0.001$), and bladder outlet obstruction (BOO) without transurethral resection of prostate (TURP) (HR 7.49, 95% CI 6.18– 9.08 $p < 0.001$) followed by BOO with TURP (HR 4.96, 95% CI 4.10-5.99 $p < 0.001$), were strong independent predictors of hospitalisation (censor-adjusted c-statistic = 0.80). The model was well-calibrated (AUC = 0.76). The global proportional hazards were met. In internal validation through bootstrapping, the model was reasonably discriminate at five (AUC 0.75) years after radiotherapy.

Conclusion. This is the first study to develop a predictive model for genitourinary toxicity requiring hospitalisation amongst men with prostate cancer treated with EBRT. Patients with localised prostate cancer and concurrent BOO may benefit from TURP before EBRT.

Keywords: “prostate cancer”, “radiotherapy”, “genitourinary toxicity”, “hospital admission”, "external beam radiotherapy", “prediction model”, “decision curve analysis”

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Introduction

Prostate cancer is the second most common malignancy amongst men worldwide and the number of long-term prostate cancer survivors continues to increase. (27) Prostate cancer is often treated with radiotherapy or surgery, with similar local control outcomes but different treatment-related toxicity profiles and side effect profiles. (279) However, there is limited high-quality data identifying predictive factors for genitourinary toxicity after radiotherapy.

The development of genitourinary toxicity following EBRT has been demonstrated to be influenced by a range of factors other than dosimetric variables alone (265, 280) and include baseline urinary symptoms (194, 262) and comorbidities such as diabetes. (199). However, predictive models classically have been limited to mechanistic analysis of dose-volume metrics, (180, 182) which are often already incorporated into radiotherapy delivery planning systems.

This study used pre-treatment clinical factors to develop and validate a novel predictive model for radiotherapy-related genitourinary toxicity requiring hospital admission, and then determined the clinical utility of the model by using decision curve analysis.

Material and Methods

Participants

The prospective South Australian Prostate Cancer Clinical Outcome Collaborative (SA-PCCOC) registry was used to identify men with localised prostate cancer who underwent local curative intent external beam radiotherapy between January 1, 1998, and January 31, 2019. The SA-PCOCC registry prospectively recruits >90% of patients who are diagnosed with prostate cancer in the State of South Australia. We linked patient records from the SA-PCCOC registry with the Integrated South Australian Activity Collection (ISAAC) Hospital Administrative Database to identify patients who presented to any major hospital in South Australia with treatment-related genitourinary toxicity, as defined by a pre-selected list of International Classification Disease 10th Edition (ICD-10-AM)/ Australian Classification of Health Interventions (ACHI). Data linkage was performed by matching patient identifiers within ENVIDO, South Australia. The list of admission and procedures codes were selected based on the literature (187) and recommendations from a multidisciplinary panel, including a urologist, radiation oncologist, general surgeon and a clinical epidemiologist. (Supplementary Table 1) A range of genitourinary toxicity events were analysed, including haematuria, irradiation cystitis, urethral stricture, urinary incontinence and urinary retention. (Supplementary Table 2)

Primary Outcomes

Of the identified patients with prostate cancer, baseline characteristics, including age (continuum), Charlson Comorbidity Index (continuum, 0/1-2/3-4/>4), diabetes mellitus (present/absent), hypertension (present/absent), smoking history (present/absent), bladder outlet obstruction (yes/ no), Transurethral resection of the prostate (TURP) before radiotherapy (yes/ no) were extracted. Patients were further categorised as having bladder outlet obstruction (BOO) with or without TURP prior to EBRT. Genitourinary Toxicity Event Free Survival (EFS) rates were then determined and compared between patient groups at increased risk of treatment-related GU toxicity.

Secondary Outcomes

Treatment-related factors, including dose (Gray; continuum and > 80Gy vs ≤ 80Gy), fractionation and date of treatment completion (< 2009 vs ≥ 2009), were extracted. Oncological characteristics, including T-stage (T1 vs T2 vs T3), ISUP grade (1 vs 2 vs 3 vs >3) and baseline Prostate-specific antigen (PSA; continuum) level were also extracted. The admission data was separated into patients who received EBRT <2009 and ≥ 2009 to account for the use of Three-dimensional conformal radiation therapy (3DCRT) and Intensity Modulated Radiotherapy/ Volumetric modulated arc therapy (IMRT/VMAT), respectively.

Statistical Analysis

Relationships between genitourinary toxicity-related hospital admission and patient, tumour or treatment characteristics were analysed using multivariable cox proportional hazard regression analysis. Regression analysis results are presented as a hazard with a 95% confidence interval. Missing

clinical data were replaced using multiple imputations by chained equations before regression analysis. (Supplementary Figure 1)

The model development process was conducted following the TRIPOD checklist. (281) Multivariable model development used a backward elimination variable selection process with 2-sided alpha = 0.05. (282) Collinearity among the variables was assessed using correlation coefficients. Diabetes was selected rather than the Charlson comorbidity score to reduce multicollinearity in the multivariable analysis. Model validation was performed by the ABCD approach put forward by Steyerberg et al. (283) The proportional hazards hypotheses were tested by Schoenfeld's residual method. The global proportional hazards assumption would not be met if we record significant associations ($p<0{\cdot}05$) for all correlation coefficients. Model discrimination was determined using a censor-adjusted c-statistic. Model calibration was demonstrated with a calibration plot generated using bootstrap resampling (n= 10,000), and the Area under the Receiver Operating Characteristic Curve (AUC) was determined. Internal validation was performed using a penalised Cox model by adaptive elastic-net regularisation, which can outperform Lasso on data with highly correlated predictors. (284) Ten-fold repeated cross-validation was used, which is a more robust internal validation method than bootstrapping (Supplementary Figure 2). (285) The model utility was assessed using Decision Curve Analysis.(286) A nomogram was developed, which incorporated the clinical predictive factors included in the final model. All statistical analyses were performed using R language, Version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria).(258)

Results

There were 3,243 patients with localised prostate cancer treated with curative intent radiotherapy included in the modelling dataset (Figure 1). Table 1 outlines the patient baseline characteristics. Patients with BOO without TURP had the lowest 10-year EFS rates (20% [95% CI 15-27%], $p < 0.001$; Figure 2, Supplementary Figure 2).

After adjusting for age, multivariable analysis revealed diabetes (HR 1.35, 95% CI 1.13-1.60, $p < 0.001$), smoking (HR 1.78, 95% CI 1.40 – 2.12, $p < 0.001$), and BOO without TURP (HR 7.49, 95% CI 6.18– 9.08 $p < 0.001$) followed by BOO with TURP ((HR 4.96, 95% CI 4.10-5.99 $p < 0.001$), to be strong independent predictors of hospitalization for treatment-related genitourinary toxicity. (Figure 2) Baseline stress urinary incontinence was a strong independent predictor in multivariable analysis (HR 3.95, 95% CI 3.28-4.75, $p <0.001$) but failed to meet the Schoenfeld proportional hazards test ($p < 0.0001$), with suspected multicollinearity with BOO and TURP, and was therefore removed from the final model.

The final model met the proportional hazards with a Global Schoenfeld Test $p = 0.1762$.

The predictive model performed well with a censor-adjusted c-statistic of 0.80. The model was reasonably discriminant at 1 (AUC 0.765) and five years (AUC 0.75), (Supplementary Figure 3), and was internally validated (Supplementary Figure 4). The decision curve analysis determined the model's utility, with a consistently greater net benefit to patients with prostate cancer at risk of radiation-induced genitourinary toxicity from threshold probability >5%. (Figure 3) A nomogram was developed to predict 5-year overall genitourinary toxicity event-free survival. (Figure 4)

Discussion

This is the first study to develop a data-driven predictive model for treatment-related genitourinary toxicity requiring hospitalisation using pre-treatment clinical characteristics amongst patients with localised prostate cancer treated by curative intent EBRT. This involved the analysis of a prospective state population-level cohort of patients (n= 3,243) with an adequate median length of follow-up (5 years), which provided valuable information regarding predictive factors for the development of treatment-related genitourinary toxicity. With the selection of hospitalisation for treatment-related toxicity as an endpoint, the model can be compared with grade 3 RTOG/ CTCAE toxicity reported in the literature. The model performed strongly in calibration at one (AUC 0.765) and five years (AUC 0.75). (Supplementary Figure 3) In addition, the model was discriminate (concordance index = 0.67, censor-adjusted c-statistic = 0.80) and is consistent with the most robust models in the literature, including the study by Yahya 2015 (concordance index 0.548-0.780). (262)

This was also the first predictive study for genitourinary toxicity requiring hospitalisation to include decision curve analysis (Figure 3) and a nomogram (Figure 4). The decision curve analysis consistently demonstrated net benefit in using the model compared to the treat-all approach above 5% threshold probability. The reliable prediction of radiotherapy-related toxicity amongst patients with prostate cancer has been valued by numerous other authors because it could guide the allocation of patients into treatment groups based on their probability of severe toxicity and improve the therapeutic ratio. (198, 287, 288) Patients at high risk of radiotherapy-related toxicity could be counselled about treatment alternatives, modifications (e.g. advanced planning corrections or dose-reduction), or deferrals. Although not statistically framed to address the question, our analysis also revealed that TURP prior to radiotherapy in patients with BOO might reduce the hazards of GU toxicity requiring admission (HR 7.49 [95% CI 6.18– 9.08[vs HR 4.96 [95% CI 4.10-5.99]).

Few other models utilise the clinical characteristics of patients with prostate cancer treated with radiotherapy to predict post-treatment toxicity. Most other models were developed in small cohorts with few toxicity-related events (n <500). (198, 274, 289) In addition, given the plethora of complex biophysical manifestations of genitourinary toxicity that can develop, other investigators focus on different toxicity outcomes: early (290) vs late (194, 198, 262) toxicity, mild or severe toxicity (based upon variable grading systems (264), RTOG/EORTC (211, 291), CTCAE (289, 291), LENT-SOMA (182, 194, 262)) or specific symptoms (194, 291, 292) including haematuria (198, 289, 291), nocturia (198), IPSS (288, 290) and erectile dysfunction (181). These perhaps have less observable impacts on the health system than hospital admissions, the outcome we have used.

Furthermore, very few predictive studies meet the TRIPOD criteria for reporting. There was inconsistent reporting of concordance index, with some reporting concordance probability estimates (182) and others AUC (198, 262, 291), creating difficulties comparing model calibration across studies. Other models were also less discriminative. (198, 262, 291) The calibration plot included in the current study appears as well calibrated as others presented in the literature. (194, 288) No other studies reported a c-statistic. Only one predictive model was externally validated (181). Whilst other models often failed to report optimism (289, 291), we used a penalised Cox model by adaptive elastic-net regularisation.

Our study has several limitations. Firstly, we did not analyse radiotherapy delivery technique (i.e. 3D-CRT IMRT, VMAT, IGRT), field size or dose-volume effect, as this data was unavailable in the current study and has already been described. (180, 182) However, the majority of included patients were treated with EBRT after 2009 (62%), indicating mostly contemporary treatment techniques. Furthermore the included clinical predictive factors remained significant in multivariable analysis adjusted for year of treatment, as demonstrated in our recently published article. (293) In addition,

we do not have information regarding baseline IPSS, prostate volume or 5-ARI or alpha-blocker medication use before EBRT. Similarly, we do not have information about whether patients received androgen deprivation therapy; however, we acknowledge that the impact of hormone therapy cannot accurately be determined given the bias to treat more unfavourable patients with hormone therapy. Finally, whilst the lack of external validation limits the generalisability of the study results, this is mitigated by using a prospectively captured state-population level dataset.

Conclusion

This study demonstrates the feasibility of predicting radiotherapy-related genitourinary toxicity requiring hospitalisation utilising pre-treatment clinical characteristics for men with localised prostate cancer. Clinicians in the pre-operative counselling setting could use our nomogram to inform patient selection and treatment-related toxicity. TURP before EBRT partially reduces the risk of genitourinary toxicity for men with prostate cancer and bladder outlet obstruction, and this relationship requires further prospective scrutiny.

Author Declarations

Competing Interests

The authors have no competing interests to declare that are relevant to the content of this article.

Ethics Approval

The SA-PCCOC database has been approved by the Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC). Approval to access the database was granted by the SA-PCCOC steering committee. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Author Contributions

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J Lee: project development and manuscript editing.

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All authors have read and approved the final manuscript.

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Chapter 7: First And Recurrent Adverse Events Requiring Hospital Admission Amongst Patients With Localised Prostate Cancer

Rowan David, MBBS ‡ †

Arman A. Kahokehr, BHB, MBChB, PGDMSc, PhD, FRACS ‡ ^

Jason Lee, MS, FRACS (Urol) ‡ †

David I. Watson, PhD, FRACS ‡

John Leung, PhD, FRANZCR ¥ ǂ

Michael E. O'Callaghan, PhD †‡ ¶^

ǂ College of Medicine and Public Health, Flinders University, Bedford Park South Australia.

† Department of Urology, Flinders Medical Centre, SA Health, Australia.

¥ GenesisCare, Adelaide, Australia

¶ South Australian Prostate Cancer Clinical Outcomes Collaborative

^ University of Adelaide, Discipline of Medicine, Freemasons Centre for Male Health and Wellbeing

Abstract

Introduction & Objectives: Men with localised prostate cancer who undergo curative intent treatment with either radical prostatectomy (RP) or external beam radiotherapy (EBRT) are at risk of treatment-related adverse effects. The incidence of late and recurrent treatment-related toxicity following EBRT in patients with prostate cancer remains under-reported. Hence, we determine the 10-year cumulative incidence of hospital admissions and recurrent admissions following EBRT and compare against patients post-RP.

Methods: We analysed a prospective population-based registry involving administrative hospital admission and cancer registry data for men who underwent primary EBRT or RP for localised prostate cancer between 2000-2020 in South Australia. Differences between the 10-year cumulative incidence of overall admission, genitourinary (GU) and gastrointestinal (GI) admissions were determined. Recurrent event analysis was performed using a Prentice-William Peterson Model adjusted for age, comorbidity and treatment year.

Results: There were 4,464 patients included, of whom all had at least one hospital admission (n= 2,359 [53%] EBRT vs n = 2,105 [47%] RP). The EBRT cohort had a higher median age (72 vs 65, $p < 0.001$), higher risk NCCN disease (52% vs 24%, $p < 0.001$) and more hormonal therapy use (44% vs 3%, $p<0.001$). EBRT was associated with a higher 10-year cumulative incidence of GU admission (40% [95% CI 35-44] EBRT vs 18% [14-21] RP, $p<0.001$) and GI admission (24% [95% CI 20-27] EBRT vs 3% [1-5] RP, $p<0.001$). The 10-year cumulative incidence of incontinence-related admission was lower after EBRT than RP (4% [95% CI 1.5-6.4] vs 8 [95% CI 6-10], $p < 0.001$). EBRT was associated with a greater risk of

recurrent overall (HR 1.80, 95% CI 1.60-2.10, p = 0.0001), GI (HR 4.62 (95% CI 1.32-16.2, p=0.02) but not GU (HR 1.25, 95% CI 0.67-2.35, p=0.5) hospital admissions.

Conclusions: The cumulative incidence of late first and recurrent admissions exceeds that associated with traditional expectations and RP.

Key Words: “Prostate cancer”; “Radiotherapy”; “Radical Prostatectomy”; “Adverse Events”; “Hospital Admission”; “Recurrent events”

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Background

Whilst the difference in overall survival associated with radical prostatectomy (RP) and external beam radiotherapy (EBRT) remains unclear (67, 69, 70), the treatment choice is often influenced by adverse event profile and patient preference. Patients with localised prostate cancer require specific information regarding the relative frequency and severity of various complications associated with these different treatment options. However, the incidence of late and recurrent treatment-related hospital admissions amongst patients with localised prostate cancer remains poorly described at a population level. These complications can compromise a patient's quality of life, primarily when occurring in the emergency setting. Accurate knowledge of the incidence of such complications following either radiotherapy or surgery would enhance patient-centred decision-making.

Hence, the primary aims of this study are to determine the 10-year cumulative incidence of overall and treatment-related first and recurrent hospital admissions at a state-population level. Patient characteristics, type and incidence of adverse events were compared among patients treated with EBRT or RP. Subgroup analysis was performed on patients treated from 2010 onwards, indicating the use of contemporary techniques.

Methods

Study Population

We analysed a state-population level cohort of patients with non-metastatic prostate cancer who underwent radical prostatectomy (open radical prostatectomy or robotic-assisted laparoscopic prostatectomy) or external beam radiotherapy, in the State of South Australia between May 1, 2000, and January 31, 2020. Data was prospectively captured by the South Australian Prostate Cancer Clinical Outcome Collaborative (SA-PCCOC) registry. The SA-PCOCC registry prospectively recruits >90% of patients diagnosed with prostate cancer in South Australia. Men treated with salvage or adjuvant radiotherapy were excluded because these treatments can lead to additional toxicity, which will be difficult to distinguish from surgical treatment-related toxicity. Men with concurrent bladder cancer (ICD-10 `C67`) were also excluded because their surveillance requires multiple cystoscopic procedures, which could be incorrectly attributed as a treatment for a prostatectomy-related complication.

We linked patient records from the SA-PCCOC registry with the Integrated South Australian Activity Collection (ISAAC) Hospital Administrative Database to identify patients admitted to any major hospital in South Australia. Treatment-related toxicity was defined by a pre-selected list of International Classification Disease 10th Edition (ICD-10-AM)/ Australian Classification of Health Interventions (ACHI). The list of admission and procedures codes was incorporated from a comprehensive literature search of published studies (187, 294, 295) and supplemented by the recommendations from a multidisciplinary expert panel, including three surgical oncologists, a radiation oncologist and a clinical epidemiologist. (Supplementary Table 1) Data linkage was performed by matching patient identifiers within Envido (Adelaide, South Australia).

Study Variable and Outcome

Patient demographics were extracted, including age at prostate cancer diagnosis, PSA at diagnosis, ISUP grade, AJCC stage, NCCN (2017) risk category, androgen deprivation therapy (ADT), treatment modality (radical prostatectomy or EBRT), treatment date, treatment-specific details (e.g. dose, fractions), ADT and mortality (i.e. the date and cause of death [e.g. prostate cancer or not prostatic cancer-related).

The primary outcomes assessed were any-cause hospital admission and treatment-related admissions. Treatment-related outcomes (TRO) were divided into genitourinary (GU) and gastrointestinal (GI). Specific genitourinary toxicity reported included urinary incontinence, urethral stricture, haematuria and urinary fistula. Specific gastrointestinal toxicity reported included proctitis/ colitis, GI stricture and fistula. (187) Admission characteristics were extracted, including readmissions, healthcare sector (private or public), admission setting (elective or emergency), and length of stay for treatment-related outcomes.

Statistical Analysis

The 10-year cumulative incidence of the first hospitalisation was determined for each toxicity category. Patients were at risk of toxicity from the date of their treatment until either the date of their first admission, last date of follow-up or death, according to the SA-PCCOC registry. Risk tables were reported to account for loss-to-follow-up. The log-rank (Mantel-Cox) test was used to determine the difference between the survival curves associated with either radiotherapy or prostatectomy.

The Prentice William-Peterson (PWP) Counting process model was used to determine a sub-hazard ratio for the risk of recurrent admission after treatment with either RP or EBRT. (296) The PWP-Counting process model was utilised because it assumes that recurrent events within a subject are related and baseline hazard varies from event to event. (296, 297) The PWP-Counting Process model was adjusted for age, Charlson score and year of treatment. Recurrent event and Mean cumulative function (MCF) estimate plots were generated to compare the trend of the recurrent events between treatment groups. MCF is also called cumulative mean function (CMF) in literature and is widely utilised in exploring recurrent event data. (298) Patient baseline and admission characteristics were summarised and compared. Categorical variables were compared using Pearson's chi-square test or Fischer Exact Test, depending on sample size. Continuous parametric and non-parametric variables were compared using the Wilcoxon rank sum test. For all statistical tests, p-values < 0.05 were considered significant.

Subgroup analysis was performed on a cohort of patients treated using contemporary techniques (i.e. RP or EBRT from 2010 onwards; Supplementary Table 1). All statistical analysis was performed using R language, Version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria). (258) The STROBE checklist was followed in reporting this observational study (Appendix 4).

Results

There were 4,464 patients with clinically localised prostate cancer, and all patients had at least one hospital admission following curative intent treatment with either primary EBRT (n= 2,359 [53%]) or RP (n = 2,105 [47%]). (Figure 1) Table 1 summarises and compares the baseline characteristics of the patients in either treatment group. The cumulative incidence of admission was initially lower in the EBRT group, especially within the first year (43% [95% CI 41-45] vs 56% [95% 54-58], p < 0.001); however, the difference diminished over time. (Figure 2, Table 2) Table 2 and Figure 2 summarise and compare the 1, 5 and 10-year cumulative incidence of hospital admissions, including genitourinary and gastrointestinal admissions. Tables 3 and 4 and Figure 3 summarise and compare the 1, 5 and 10-year cumulative incidence of specific genitourinary and gastrointestinal toxicity. EBRT was associated with a greater proportion of emergency admission (8,112 [36%] vs 3,964 (27%), p<0.001), greater median (IQR) inpatient length of stay (3 [1-8] vs 2 [1-5], p < 0.001) and number of admissions (20 [9-75] vs 14 [6-52], p < 0.001; Table 5). EBRT was associated with a significantly greater risk of recurrent hospital admissions overall (HR 1.80, 95% CI 1.60-2.10, p = 0.0001) and admissions related to GI toxicity (HR 4.62 (95% CI 1.32-16.2, p=0.02), after adjustment for Charlson score and treatment year. However, there was no statistically significant difference in recurrent admissions related to GU toxicity between treatment groups (HR 1.25, 95% CI 0.67-2.35, p=0.5). (Figure 4, Table 6)

Amongst patients treated by contemporary techniques (n=2,673 [n= 1,462 RP vs n=1,211 EBRT]; Appendix 2), EBRT after 2010 was associated with a higher 10-year cumulative incidence of GU (40% [95% 25-52%] vs 17% [11-23%], p=0.001) and GI (18% [13-23%] vs 3.4% [1.1-5.6%], p < 0.001) hospital admissions compared to RP after 2010. (Table 3) EBRT after 2010 was associated with a higher 10-year cumulative incidence of haematuria (30% [95% 13-44%] vs 5.6% [3.1-8.1%], p<0.001) and urinary fistula (0.6% [<0.1-1.2%] vs 0% [0-0%], p = 0.045) admissions. RP ≥ 2010 was associated with a higher

10-year cumulative incidence of urinary incontinence (0.6% [95% CI 0.2-1.0] vs <0.1 [95% CI 0.2-1.0], p < 0.001)

Compared to EBRT before 2010 (n=1,088 [47%]), patients treated with EBRT after 2010 (n=1,250 [53%]) had a higher 10-year cumulative incidence of any hospital admission (100% [95% CI 100-100] vs 97% [95% CI 96-95%], p < 0.001) and GU-related admission (36% [95% CI 31-40] vs 19% [18-21], p < 0.001). Furthermore, there was no significant difference in the 10-year cumulative incidence of GI-related admission (9% [95% CI 8-10] vs 10% [9-10], p = 0.2; Supplementary Table 2)

Discussion

This is the first population-level study of patients with clinically localised prostate cancer treated with contemporary techniques (RP or EBRT performed from 2010 onwards) to compare the 10-year cumulative incidence of specific treatment-related toxicity and recurrent events. Amongst patients treated by contemporary techniques (Appendix 2), EBRT after 2010 was associated with a significantly higher 10-year cumulative incidence of GU and GI hospital admissions compared to RP after 2010. (Table 3) EBRT after 2010 was associated with a significantly higher 10-year cumulative incidence of haematuria and urinary fistula-related admissions compared to RP after 2010. Whilst RP after 2010 was associated with a significantly higher 10-year cumulative incidence of urinary incontinence than EBRT after 2010.

In addition, this is also the first study to model recurrent adverse events in patients with localised prostate cancer. Overall, EBRT was associated with significantly higher median (IQR) recurrent admissions (Table 5) and higher proportions of emergency admissions (Table 5). EBRT was associated with a significantly greater risk of recurrent overall and GI-related hospital admissions after adjustment for age, Charlson score and treatment year. (Table 6)

The 10-year cumulative incidence of GU-related first hospital admission was higher amongst men treated with EBRT than RP. The 10-year cumulative incidence estimates of GU toxicity in the current study exceed the 5-year estimates reported in the literature. (187) The only other population study (n= 16,595 radiotherapy vs n= 15,870 RP) to comprehensively compare the incidence of specific-treatment-related complications after RP or radiotherapy for clinically localised prostate cancer, similarly reported a higher 5-year rate of treatment-related admission following radiotherapy (27.1% 95% CI (26.4-27.9) and 17.5% 95% CI (16.9-18.1); adjusted HR 2.08-10.8 ($p < 0.0001$)). (187) However, this study was limited by the inclusion of a heterogenous radiotherapy group, including brachytherapy

and stereotactic radiotherapy, and mostly outdated EBRT techniques (76% 3D-CRT) and five-year outcome data. (187)

EBRT was associated with a higher 10-year cumulative incidence of haematuria-related admission (27% [95% CI 22-31] vs 7% [95% 4-9, p <0.001]) than RP. Similarly, Nam et al. reported that compared to RP, patients treated by EBRT had higher frequency distribution (575 (14·3%) vs 165 (6·0%)) and risk in person-years (11·1/1000 vs 2·8/1000). (187)

EBRT was associated with a higher 10-year cumulative incidence of stricture-related admission (24% [95% CI 20-27] vs 11% [95% CI 9-14], p = 0.008) than RP. Similarly, Nam et al. reported that compared to RP, patients treated by EBRT had lower frequency distribution (12·1% vs 72·8%) and risk in person-years of urinary obstruction (9·4/1000 vs 33·5/1000). The need for long-term follow-up of lower urinary tract symptoms was highlighted by the recent meta-analysis by Awad et al. (214), which found that an increase in median follow-up time after prostate EBRT led to a significantly increased risk of developing urethral strictures (OR 0.005, 95% CI 0.0002-0.01, p = 0.041).

EBRT was associated with a higher 10-year cumulative incidence of GI toxicity-related admission (24% [95% CI 20-27] vs 3% [1-5], p<0.001), including colitis (23% [20-26] vs 2% [0.8-3.1], p<0.001). Similarly, Nam RK et al.(187) reported that compared to RP, patients treated with EBRT had higher frequency distribution (553 (13·7%) vs 0) and risk in person-years (10·0/1000 vs 0) of GI toxicity. (187)

RP was associated with a higher 10-year cumulative incidence of incontinence-related admission [8 [95% CI 6-10] vs 4% [95% CI 1.5-6.4], p < 0.001). The need for follow-up to 15 years post-radiotherapy was demonstrated by Resnick et al., which compared patients with localised prostate cancer treated between 1994-1995 with either RP (n=1164) or EBRT (n=491) and revealed significantly higher five and ten-year rates of urinary incontinence after RP, but no significant difference at 15-years of follow-up (p

> 0.05). (299) Unfortunately, this study did not assess non-functional outcomes or hospitalisation or surgical operation rates.

There was no statistically significant difference in the 10-year cumulative incidence of GU fistula-related admission associated with EBRT or RP (2% [95% CI 0-4.5%] vs 0.2% [95% CI 0-0.6%], p=0.054. However, Nam et al. reported that compared to RP, patients treated by EBRT had lower frequency distribution (12 (0·3%) vs 30 (1·1%)) and risk in person-years (0·2/1000 vs 0·5/1000) of pelvic fistula. (187)

This study has several limitations. Hospital admissions may be underreported as patients managed in other states for treatment-related complications were not captured in our state-based registry. By using hospital and procedure codes as a surrogate for urinary complications, patients who were symptomatic but did not undergo hospitalisation or a procedure for their symptoms were not captured and absent from our analysis. Functional complications, such as urinary incontinence, will likely be underestimated in our cumulative incidence analysis. Whilst the diagnosis of haemorrhagic radiation-induced cystitis cannot be confirmed in our study, these rates exceed the reported estimates in the literature, ranging from 2.6% to 12.1%. (159-161, 187) Furthermore, the SA-PCOCC database does not collect information on prescription drugs. Other complications related to androgen deprivation, such as cardiovascular events, will need to be assessed in future studies. Whilst the SA-PCOCC registry lacks data on EBRT delivery technique, several other studies have also reported an inconsistent reduction in treatment-related late GU toxicity despite technological improvements in prostate EBRT delivery (i.e. intensity-modulated radiotherapy and image-guided radiotherapy. (114-116, 294) The study also does not include a comparison of other forms of radiotherapy, such as brachytherapy.

In summary, amongst patients with clinically localised prostate cancer, curative-intent EBRT was associated with a significantly higher 10-year cumulative incidence of genitourinary and gastrointestinal toxicity-related admissions compared to RP. EBRT use was associated with a significantly greater risk of recurrent hospital admissions despite improvements in radiotherapy delivery technique and adjustment for age and comorbidity.

Author Declarations

Competing Interests

The authors have no competing interests to declare that are relevant to the content of this article.

Ethics Approval

The SA-PCCOC database has been approved by the Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC). The SA-PCCOC steering committee granted approval to access the database. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Author Contributions

RV David: project development, data collection, data analysis and manuscript writing.

AA Kahokehr: data analysis and manuscript editing.

J Lee: project development and manuscript editing.

J Leung: data analysis and manuscript editing.

DI Watson: project development and manuscript editing.

ME O'Callaghan: project development, data analysis and manuscript editing.

All authors have read and approved the final manuscript.

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Figures

Figure 1. Flow Chart of Patient Selection Process

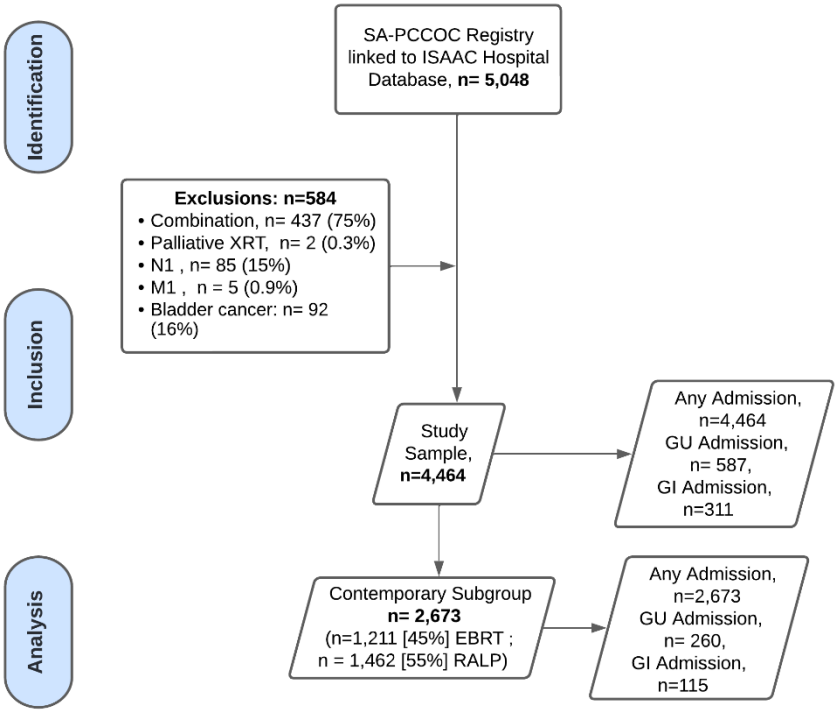


Figure 2. 10-year Cumulative Incidence of First Hospital Admission Following Curative Treatment For Clinically Localised Prostate Cancer

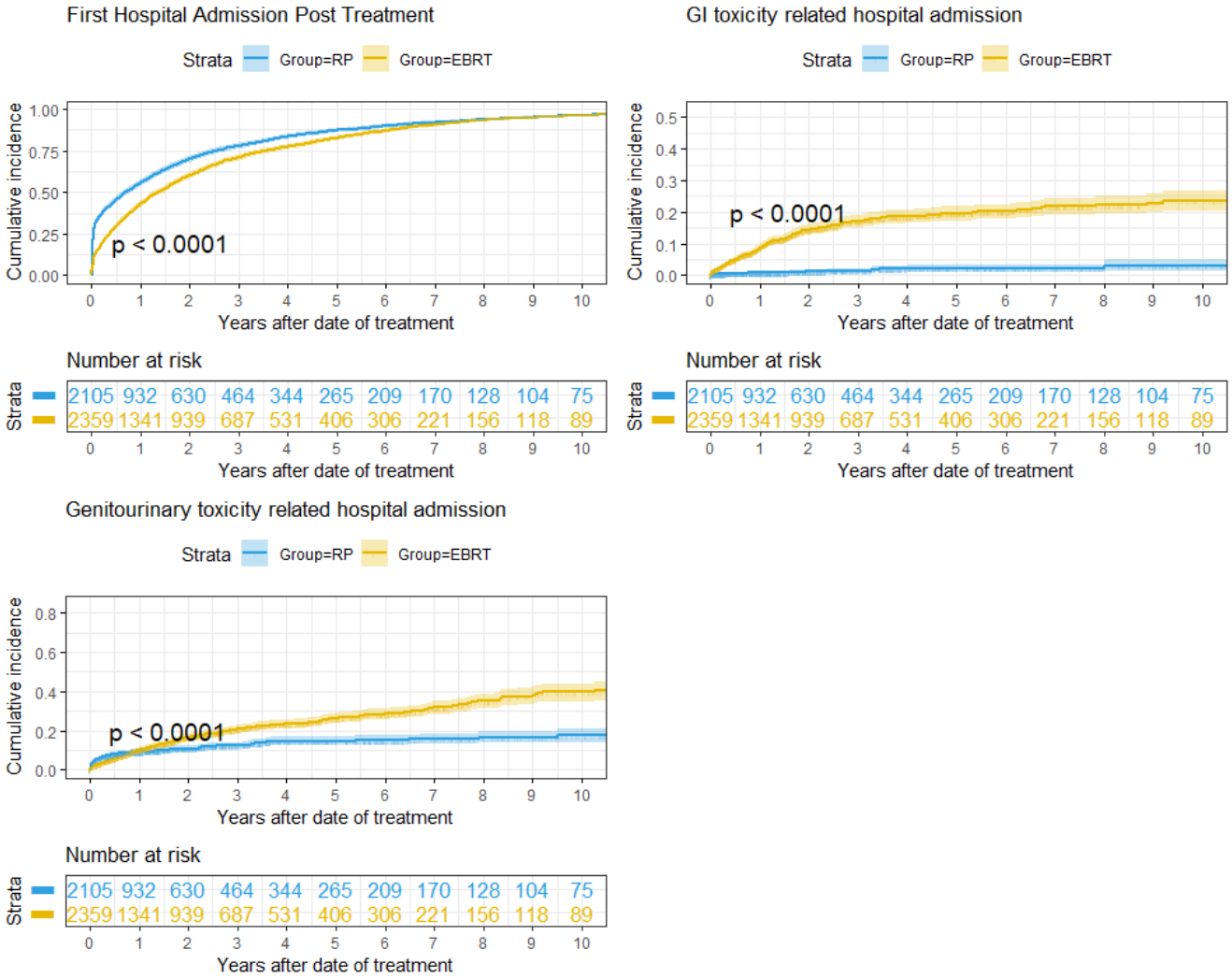


Figure 3. 10-year Cumulative Incidence of First Treatment-Related Specific Toxicity

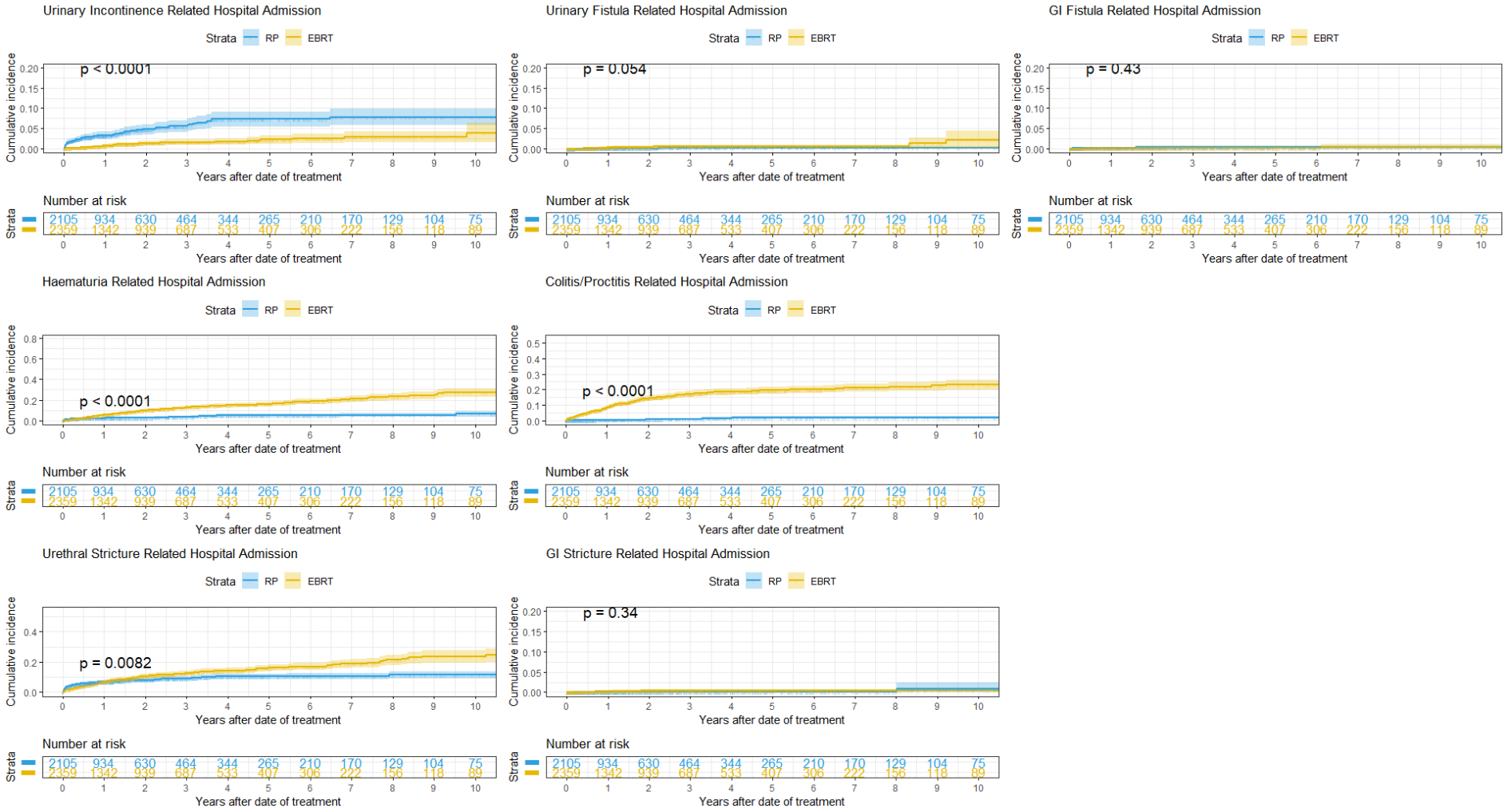
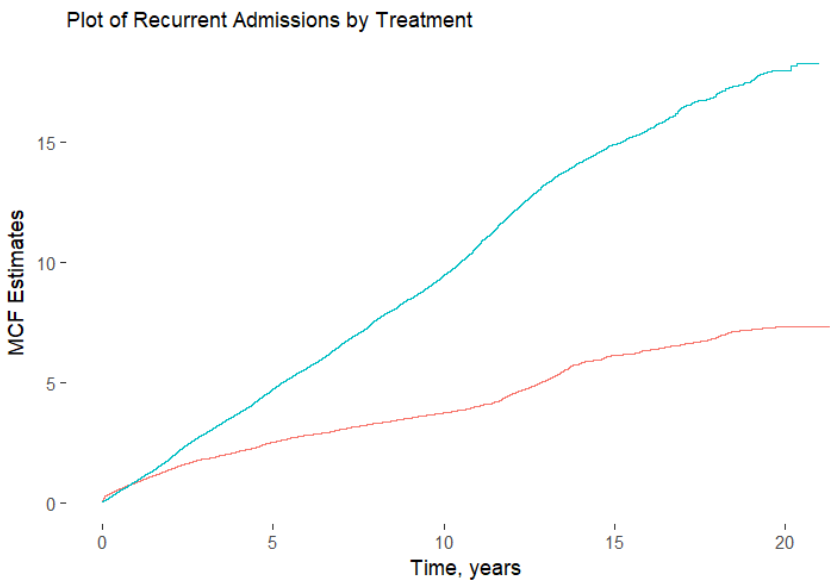
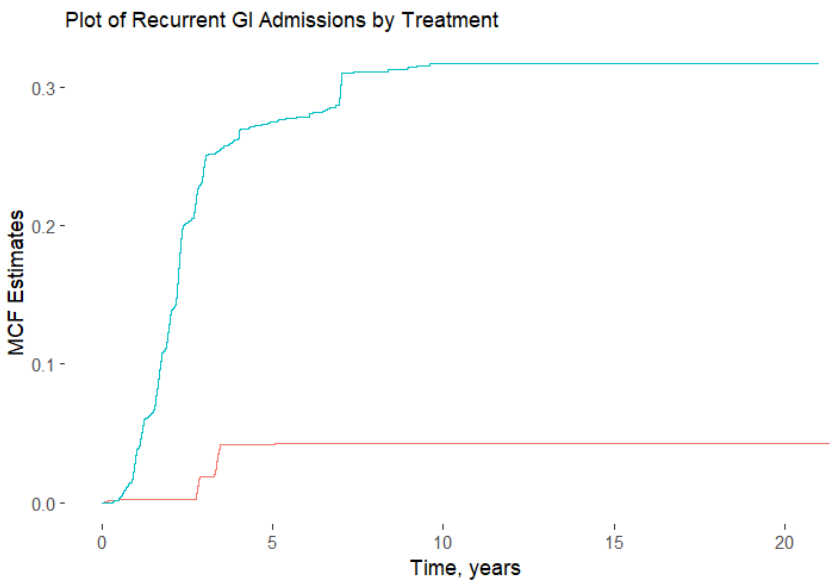


Figure 4. Mean Cumulative Function Estimates for Recurrent Admissions by Treatment


Plot of Recurrent Admissions by Treatment
MCF Estimates
0
5
10
15
0
5
10
15
20
Time, years


Plot of Recurrent GI Admissions by Treatment
MCF Estimates
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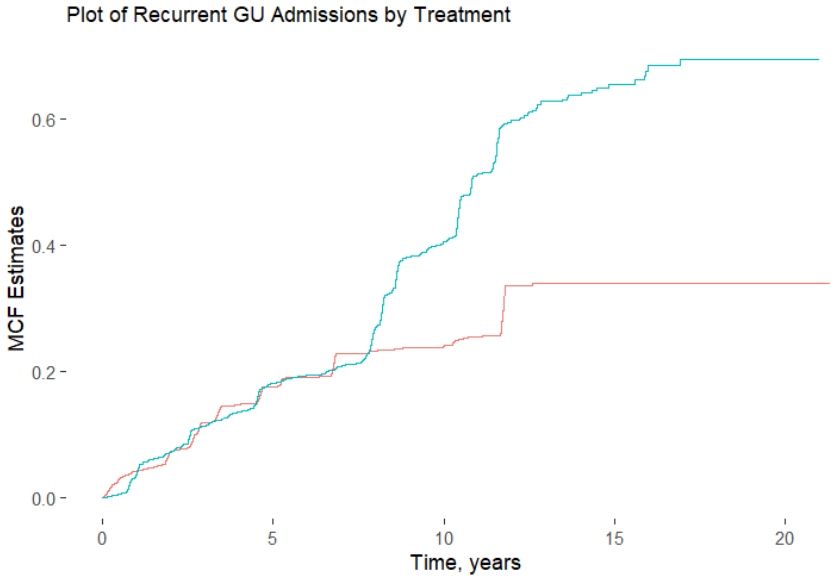
0.1
0.2
0.3
0
5
10
15
20
Time, years


Plot of Recurrent GU Admissions by Treatment
MCF Estimates
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0.2
0.4
0.6
0
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10
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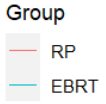
20
Time, years


Group
RP
EBRT

Tables

Table 1. Baseline Characteristics of Patients with Localised Prostate Cancer with a Hospital Admission Post-treatment.

		Treatment modality		
Characteristic	Overall, N = 4,464[1]	RP, N = 2,105[1]	EBRT, N = 2,359[1]	p-value
Any Hospital Admission	4,464 (100%)	2,105 (100%)	2,359 (100%)	
GU Admission	587 (13%)	185 (8.8%)	402 (17%)	<0.001[2]
Urinary Stricture Admission	367 (8.2%)	129 (6.1%)	238 (10%)	<0.001[2]
GU Fistula Admission	13 (0.3%)	2 (<0.1%)	11 (0.5%)	0.022[2]
Haematuria	289 (6.5%)	54 (2.6%)	235 (10.0%)	<0.001[2]
Urinary Incontinence	103 (2.3%)	74 (3.5%)	29 (1.2%)	<0.001[2]
GI Admission	311 (7.0%)	21 (1.0%)	290 (12%)	<0.001[2]
Proctitis or Colitis	299 (6.7%)	14 (0.7%)	285 (12%)	<0.001[2]
GI Stricture Admission	8 (0.2%)	2 (<0.1%)	6 (0.3%)	0.29[3]
GI Fistula Admission	9 (0.2%)	5 (0.2%)	4 (0.2%)	0.74[3]
Age at diagnosis	68 (63, 73)	65 (60, 69)	72 (66, 76)	<0.001[4]
NCCN Risk Category				<0.001[2]
High	1,596 (38%)	448 (22%)	1,148 (52%)	
Intermediate	1,718 (41%)	961 (48%)	757 (35%)	

		Treatment modality		
Characteristic	Overall, N = 4,464[1]	RP, N = 2,105[1]	EBRT, N = 2,359[1]	p-value
Low	889 (21%)	605 (30%)	284 (13%)	
(Missing)	261	91	170	
Median (IQR) CCI	3 (2, 3)	2 (2, 3)	3 (2, 4)	<0.001[4]
iPSA Level				<0.001[2]
<4	300 (7.7%)	199 (10%)	101 (5.1%)	
4-10	2,201 (56%)	1,346 (70%)	855 (43%)	
>10	1,395 (36%)	381 (20%)	1,014 (51%)	
(Missing)	568	179	389	
ISUP Grade				<0.001[2]
1	1,522 (35%)	827 (40%)	695 (31%)	
2	1,262 (29%)	701 (34%)	561 (25%)	
3	709 (16%)	299 (15%)	410 (18%)	
>3	836 (19%)	226 (11%)	610 (27%)	
(Missing)	135	52	83	
ADT	1,084 (24%)	45 (2.1%)	1,039 (44%)	<0.001[2]
Operation type				

		Treatment modality		
Characteristic	Overall, N = 4,464[1]	RP, N = 2,105[1]	EBRT, N = 2,359[1]	p-value
ORRP	612 (29%)	612 (29%)	NA (NA%)	
RALP	1,475 (71%)	1,475 (71%)	NA (NA%)	
(Missing)	2,377	18	2,359	
Dose Gy	74 (70, 78)	NA (NA, NA)	74 (70, 78)	
(Missing)	2,294	NA	189	
Fractions	37 (35, 39)	NA (NA, NA)	37 (35, 39)	
(Missing)	2,296	NA	191	
Treatment Period				<0.001[2]
<2010	1,730 (39%)	642 (31%)	1,088 (47%)	
≥2010	2,712 (61%)	1,462 (69%)	1,250 (53%)	
(Missing)	22	1	21	
Follow up years	7.2 (4.1, 11.5)	6.8 (4.2, 11.6)	7.5 (3.9, 11.4)	0.57[4]
Mortality				<0.001[2]
Alive	3,118 (70%)	1,859 (88%)	1,259 (53%)	
Dead	1,346 (30%)	246 (12%)	1,100 (47%)	
Cause of Death				<0.001[2]

		Treatment modality		
Characteristic	Overall, N = 4,464[1]	RP, N = 2,105[1]	EBRT, N = 2,359[1]	p-value
Other	935 (69%)	193 (78%)	742 (67%)	
Prostate cancer	411 (31%)	53 (22%)	358 (33%)	
Alive	3,118	1,859	1,259	

[1]n (%); Median (IQR), [2]Pearson's Chi-squared test, [3]Fisher's exact test, [4]Wilcoxon rank sum test

Bolded values were considered statistically significant at $p < 0.05$

Abbreviations: CCI, Charlson Comorbidity Score

Table 2. Cumulative Incidence of First Admission

	Any				GU				GI			
Characteristic	1 Year	5 Year	10 Year	p-value[1]	1 Year	5 Year	10 Year	p-value[1]	1 Year	5 Year	10 Year	p-value[1]
Group				<0.001				<0.001				<0.001
RP	56% (54%,58%)	87% (86%,89%)	96% (96%,97%)		9.2% (7.7%,11%)	15% (13%,17%)	18% (14%,21%)		0.8% (0.3%,1.3%)	2.4% (1.2%,3.6%)	3.1% (1.2%,5.0%)	
EBRT	43% (41%,45%)	83% (81%,84%)	96% (95%,97%)		10% (8.8%,12%)	26% (24%,29%)	40% (35%,44%)		8.6% (7.3%,9.9%)	20% (17%,22%)	24% (20%,27%)	
≥ 2010				>0.9				0.001				<0.001
RP	3.5% (2.4%,4.7%)	7.9% (5.1%,11%)	7.9% (5.1%,11%)		7.3% (5.7%,8.9%)	15% (11%,18%)	17% (11%,23%)		0.8% (0.2%,1.4%)	3.4% (1.1%,5.6%)	3.4% (1.1%,5.6%)	
EBRT	2.2% (1.1%,3.2%)	11% (7.1%,14%)	17% (9.6%,25%)		10% (8.3%,13%)	26% (22%,30%)	40% (25%,52%)		8.2% (6.3%,10%)	16% (12%,19%)	18% (13%,23%)	

	Any				GU				GI			
Characteristic	1 Year	5 Year	10 Year	p-value[1]	1 Year	5 Year	10 Year	p-value[1]	1 Year	5 Year	10 Year	p-value[1]
< 2010				0.3				0.005				<0.001
RP	48% (44%,52%)	70% (66%,74%)	89% (86%,91%)		13% (10%,16%)	17% (13%,21%)	20% (15%,24%)		0.8% (<0.1%,1.6%)	1.6% (0.2%,2.9%)	2.4% (0.3%,4.6%)	
EBRT	30% (27%,32%)	72% (69%,74%)	92% (90%,93%)		8.7% (6.9%,10%)	25% (22%,29%)	39% (33%,44%)		8.6% (6.8%,10%)	22% (19%,25%)	26% (22%,30%)	

[1]Log-rank test

Table 3. Cumulative Incidence of First Admission Related to Specific Urinary Toxicity

	Haematuria				Urinary Stricture				Urinary Incontinence				Urinary Fistula			
Characteristic	1 Year	5 Year	10 Year	p-value[1]	1 Year	5 Year	10 Year	p-value[1]	1 Year	5 Year	10 Year	p-value[1]	1 Year	5 Year	10 Year	p-value[1]
Group				<0.001				0.008				<0.001				0.054
RP	2.4% (1.7%, 3.2%)	4.8% (3.3%, 6.3%)	6.5% (3.6%, 9.2%)		6.7% (5.5%, 8.0%)	10% (8.5%, 12%)	11% (9.0%, 14%)		3.3% (2.4%, 4.2%)	7.4% (5.5%, 9.2%)	7.8% (5.8%, 9.9%)		<0.1% (0%, 0.2%)	0.2% (0%, 0.6%)	0.2% (0%, 0.6%)	
EBRT	5.8% (4.7%, 6.8%)	16% (14%, 18%)	27% (22%, 31%)		7.0% (5.8%, 8.1%)	16% (14%, 18%)	24% (20%, 27%)		0.7% (0.3%, 1.2%)	2.3% (1.3%, 3.2%)	4.0% (1.5%, 6.4%)		0.4% (<0.1%, 0.6%)	0.6% (0.2%, 1.0%)	2.2% (0%, 4.5%)	
≥ 2010				<0.001				0.056				<0.001				0.045

	Haematuria				Urinary Stricture				Urinary Incontinence				Urinary Fistula			
Characteristic	1 Year	5 Year	10 Year	p-value[1]	1 Year	5 Year	10 Year	p-value[1]	1 Year	5 Year	10 Year	p-value[1]	1 Year	5 Year	10 Year	p-value[1]
RP	2.3% (1.4%, 3.2%)	5.6% (3.1%, 8.1%)	5.6% (3.1%, 8.1%)		4.8% (3.4%, 6.1%)	9.7% (6.8%, 12%)	9.7% (6.8%, 12%)		0% (0%, 0%)	0.1% (0%, 0.3%)	0.6% (0.2%, 1.0%)		0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	
EBRT	6.4% (4.7%, 8.1%)	16% (12%, 20%)	30% (13%, 44%)		6.5% (4.8%, 8.2%)	14% (11%, 18%)	28% (11%, 42%)		0% (0%, 0%)	0% (0%, 0%)	<0.1% (0%, 0.3%)		0.4% (0%, 0.9%)	0.6% (<0.1%, 1.2%)	0.6% (<0.1%, 1.2%)	
< 2010				<0.001				0.7				<0.001				0.4
RP	2.8% (1.2%, 4.2%)	4.3% (2.2%, 6.3%)	6.1% (2.7%, 9.3%)		11% (8.2%, 14%)	14% (10%, 17%)	15% (11%, 18%)		4.0% (2.2%, 5.8%)	6.3% (3.7%, 8.8%)	6.3% (3.7%, 8.8%)		0.3% (0%, 0.8%)	0.6% (0%, 1.5%)	0.6% (0%, 1.5%)	

	Haematuria				Urinary Stricture				Urinary Incontinence				Urinary Fistula			
Characteristic	1 Year	5 Year	10 Year	p-value[1]	1 Year	5 Year	10 Year	p-value[1]	1 Year	5 Year	10 Year	p-value[1]	1 Year	5 Year	10 Year	p-value[1]
EBRT	4.5% (3.1%, 5.8%)	16% (13%, 18%)	26% (21%, 31%)		6.3% (4.7%, 7.9%)	16% (13%, 19%)	23% (18%, 27%)		0.8% (0.2%, 1.4%)	2.5% (1.2%, 3.7%)	4.4% (1.7%, 7.0%)		0.3% (0%, 0.6%)	0.6% (<0.1%, 1.2%)	2.3% (0%, 4.7%)	

[1]Log-rank test

Table 4. Cumulative Incidence Tables For First Admission Related to Specific GI Toxicity

	Colitis				GI Stricture				GI Fistula			
Characteristic	1 Year	5 Year	10 Year	p-value[1]	1 Year	5 Year	10 Year	p-value[1]	1 Year	5 Year	10 Year	p-value[1]
Group				<0.001				0.3				0.4
RP	0.5% (0.1%, 0.9%)	1.9% (0.8%, 3.1%)	1.9% (0.8%, 3.1%)		<0.1% (0%, 0.2%)	<0.1% (0%, 0.2%)	0.9% (0%, 2.4%)		0.2% (0%, 0.5%)	0.4% (<0.1%, 0.7%)	0.4% (<0.1%, 0.7%)	
EBRT	8.5% (7.2%, 9.7%)	19% (17%, 22%)	23% (20%, 26%)		0.2% (<0.1%, 0.5%)	0.4% (<0.1%, 0.7%)	0.4% (<0.1%, 0.7%)		0.2% (0%, 0.3%)	0.2% (0%, 0.3%)	0.5% (0%, 1.2%)	
≥ 2010				<0.001				0.6				>0.9
RP	0.5% (<0.1%, 1.0%)	3.1% (0.8%, 5.3%)	3.1% (0.8%, 5.3%)		0.1% (0%, 0.3%)	0.1% (0%, 0.3%)	0.1% (0%, 0.3%)		0.2% (0%, 0.5%)	0.2% (0%, 0.5%)	0.2% (0%, 0.5%)	
EBRT	8.1% (6.2%, 9.9%)	16% (12%, 19%)	18% (13%, 23%)		0.1% (0%, 0.4%)	0.3% (0%, 0.8%)	0.3% (0%, 0.8%)		0.2% (0%, 0.4%)	0.2% (0%, 0.4%)	0.2% (0%, 0.4%)	

	Colitis				GI Stricture				GI Fistula			
Characteristic	1 Year	5 Year	10 Year	p-value[1]	1 Year	5 Year	10 Year	p-value[1]	1 Year	5 Year	10 Year	p-value[1]
< 2010				<0.001				0.5				
RP	0.4% (0%, 1.1%)	0.9% (0%, 1.9%)	0.9% (0%, 1.9%)		0% (0%, 0%)	0% (0%, 0%)	0.9% (0%, 2.6%)		0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	
EBRT	8.4% (6.6%, 10%)	21% (18%, 24%)	25% (21%, 29%)		0.3% (0%, 0.7%)	0.5% (0%, 1.0%)	0.5% (0%, 1.0%)		0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	

[1]Log-rank test

Table 5. Hospital Admissions for GI or GU toxicity comparing RP and EBRT

		Treatment modality		
Event	Overall, N = 37,136[1]	1.RP, N = 14,423[1]	2.EBRT, N = 22,713[1]	p-value
Median (IQR) Admissions	18 (7, 67)	14 (6, 52)	20 (9, 75)	<0.001[2]
TRO Admission	3,289 / 37,136 (8.9%)	974 / 14,423 (6.8%)	2,315 / 22,713 (10%)	<0.001[3]
TRO Readmission	3,000 / 37,136 (8.1%)	879 / 14,423 (6.1%)	2,121 / 22,713 (9.3%)	<0.001[3]
GU Admission	2,265 / 37,136 (6.1%)	928 / 14,423 (6.4%)	1,337 / 22,713 (5.9%)	0.032[3]
Haematuria Admission	1,378 / 37,136 (3.7%)	552 / 14,423 (3.8%)	826 / 22,713 (3.6%)	0.3[3]
GU Stricture Admission	835 / 37,136 (2.2%)	337 / 14,423 (2.3%)	498 / 22,713 (2.2%)	0.4[3]
UI Admission	191 / 37,136 (0.5%)	156 / 14,423 (1.1%)	35 / 22,713 (0.2%)	<0.001[3]
GU Fistula Admission	65 / 37,136 (0.2%)	5 / 14,423 (<0.1%)	60 / 22,713 (0.3%)	<0.001[3]
GI Admission	1,131 / 37,136 (3.0%)	147 / 14,423 (1.0%)	984 / 22,713 (4.3%)	<0.001[3]
Colitis Admission	1,108 / 37,136 (3.0%)	137 / 14,423 (0.9%)	971 / 22,713 (4.3%)	<0.001[3]
GI Stricture Admission	10 / 37,136 (<0.1%)	2 / 14,423 (<0.1%)	8 / 22,713 (<0.1%)	0.3[4]
GI Fistula Admission	14 / 37,136 (<0.1%)	8 / 14,423 (<0.1%)	6 / 22,713 (<0.1%)	0.2[3]
Healthcare Sector				<0.001[3]
Private	6,728 / 37,136 (18%)	5,005 / 14,423 (35%)	1,723 / 22,713 (7.6%)	
Public	30,408 / 37,136 (82%)	9,418 / 14,423 (65%)	20,990 / 22,713 (92%)	

		Treatment modality		
Event	Overall, N = 37,136[1]	1.RP, N = 14,423[1]	2.EBRT, N = 22,713[1]	p-value
Admission Setting				<0.001[3]
Elective	15,121 / 37,136 (41%)	7,173 / 14,423 (50%)	7,948 / 22,713 (35%)	
Emergency	12,076 / 37,136 (33%)	3,964 / 14,423 (27%)	8,112 / 22,713 (36%)	
Not Applicable	9,939 / 37,136 (27%)	3,286 / 14,423 (23%)	6,653 / 22,713 (29%)	
Median (IQR) LOS for TRO, days	3 (1, 7)	3 (1, 6)	3 (1, 7)	0.062[4]

[1]n / N (%),[2]Wilcoxon rank sum test, [3]Pearson's Chi-squared test, [4]Fisher's exact test

Bolded values are statistically significant at $p < 0.05$

Abbreviations: TRO, Treatment-Related Outcome; GU, Genitourinary; UI, Urinary Incontinence; GI, Gastrointestinal; LOS, Length of Stay

Table 6 Recurrent Events Multivariable Prentice William Peterson Counting Process Regression Model

Characteristic	HR[1]	95% CI[1]	p-value
Any Recurrent Admission			
EBRT	1.26	1.04, 1.53	0.016
Year	1.13	1.11, 1.15	<0.001
Charlson Score	1.08	1.03, 1.12	<0.001
Recurrent GI Admission			
EBRT	4.62	1.32, 16.2	0.017
Year	1.02	0.94, 1.10	0.6
Charlson Score	0.84	0.59, 1.19	0.3
Recurrent GU Admission			
EBRT	1.25	0.67, 2.35	0.5
Year	1.13	1.05, 1.22	0.001
Charlson Score	0.69	0.54, 0.87	0.002

[1]HR = Hazard Ratio, CI = Confidence Interval

Bolded values are considered statistically significant at $p < 0.05$.

Chapter 8: Patient-Reported Outcomes Measures Following External Beam Radiotherapy Or Radical Prostatectomy In Localised Prostate Cancer.

Rowan V. David, MBBS ‡ † ORCID 0000-0003-4483-1204

Arman A. Kahokehr, PhD, FRACS ‡ ^ ORCID 0000-0003-2618-3266

Jason Lee, MS, FRACS (Urol) ‡ †

David I. Watson, PhD, FRACS ‡ ORCID 0000-0002-7683-2693

John Leung, PhD, FRANZCR ¥ ǂ ORCID 0000-0003-1834-9131

Michael E. O'Callaghan, PhD ‡ † ¶^ ORCID 0000-0001-5038-5859

‡ College of Medicine and Public Health, Flinders University, Bedford Park South Australia.

† Department of Urology, Flinders Medical Centre, SA Health, Australia.

¥ GenesisCare, Adelaide, Australia

¶ South Australian Prostate Cancer Clinical Outcomes Collaborative

^ University of Adelaide, Discipline of Medicine, Freemasons Centre for Male Health and Wellbeing

Abstract

Introduction & Objectives: Late toxicity following radiotherapy is common and can compromise patient quality of life. However, the impact of toxicity on patient-reported outcomes measures (PROMS) five-years after prostate external beam radiotherapy (EBRT) is poorly characterised. Hence, we describe Expanded Prostate Cancer Index Composite (EPIC-26) five years post EBRT and compare against radical prostatectomy (RP).

Methods: A prospective cohort of patients with localised prostate cancer treated between 2000 and 2020 captured by a state-level cancer registry was analysed. Multivariable mixed effects linear was performed. The percentage of patients recording a decline in EPIC-26 domains compared with baseline which exceeded the minimal clinically important difference (MCID) was calculated and compared between groups. Subgroup analysis was performed on patients treated using contemporary techniques.

Results: There were 1,720 patients (EBRT n= 1,441 vs RP n = 279) with evaluable EPIC-26 PROMS. Patients in the EBRT group had higher median age (74 vs 66, p <0.001) and NCCN high-risk disease (61% vs 24%, p < 0.001). Bowel domain scores were worse after EBRT compared to RP (beta -0.46, 95% CI -1.20 - -0.28, p<0.001), with a greater proportion of patients reporting a change in symptoms that exceeded the MCID at 12 months (22 vs 11%, p=0.009). Moderate/big bowel bother scores were significantly higher in the EBRT cohort at baseline and all follow-up periods compared to RP (beta -8.27, 95% CI -10.21- -6.34, p<0.001). Pad use (i.e. ≥ 1) per day significantly lower amongst the EBRT group (beta 16.56, 95% CI 14.35 - 18.76, p<0.001). Despite contemporary techniques, EBRT was

associated worse bowel domain scores at 12 (75 vs 80, $p<0.05$) and 60 months (75 vs 80, $p<0.05$) than RP.

Conclusion: There are significant differences in PROMs after local curative treatment for prostate cancer which persist to five years post treatment, despite contemporary techniques. Understanding the associated toxicity patterns could inform shared decision-making during pre-treatment counselling.

Key Words: “Prostate cancer”; “Radiotherapy”; “Radical Prostatectomy”; “Patient Reported Outcome Measures”; “EPIC-26”; “Quality of Life”

Abstract Word Count: 311

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Background

Patients with localised prostate cancer who undergo either primary external beam radiotherapy (EBRT) or radical prostatectomy (RP) often suffer treatment-related adverse effects which impair patient quality of life. A growing population of men is at risk of developing these adverse effects because of the increasing incidence of the disease, the ageing population, and the prolonged survival following treatment. (175) The importance of patient-reported outcome measures (PROMs) has been demonstrated by multiple studies which demonstrate their superior accuracy in determining the incidence of treatment-related adverse events compared to clinician-reported outcomes. (300, 301) However, there is a lack of high-quality population-level studies which compare PROMs following EBRT or RP in patients with localised prostate cancer. (302) There are very few studies that have included five-year follow-up outcomes. (175, 303) In addition, there are few population-based comparative studies, (175, 304, 305) of which most lack a validated PROM instrument, (175, 304) or contained heterogenous radiotherapy treatments (e.g. adjuvant/ salvage treatment, combination EBRT + Brachytherapy). (303, 304)

Hence, the primary aim of this study is to describe five-year PROMs post primary curative intent EBRT alone for localised prostate cancer and to compare outcomes against patients treated with radical prostatectomy. The secondary aims are to describe and compare baseline characteristics between the groups and to perform subgroup analysis on a cohort of patients treated using contemporary techniques.

Methods

Study Population

We analysed a state-population level cohort of patients with non-metastatic prostate cancer who underwent radical prostatectomy (open radical retropubic prostatectomy [ORRP] or robotic-assisted laparoscopic prostatectomy [RALP]) or EBRT in South Australia between January 1, 1998, and January 31, 2019, as prospectively captured by the South Australian Prostate Cancer Clinical Outcome Collaborative (SA-PCCOC) registry. The SA-PCOCC registry prospectively recruits >90% of patients diagnosed with prostate cancer in South Australia. Patients were invited to complete the EPIC-26 quality of life questionnaire via a paper-based survey at diagnosis and 3, 6, 12-, 24- and 60 months post-diagnosis. Men treated with salvage or adjuvant radiotherapy were excluded because these treatments can lead to additional toxicity. Men with concurrent bladder cancer (ICD-10-AM code `C67`) were also excluded.

Study Variable and Outcome

EPIC-26 function domain scores and bother symptoms were reported separately. (306) EPIC-26 domain scores were determined for urinary continence, urinary irritation/obstruction, bowel, sexual and hormonal function and presented as a 0-100 score. Higher domain scores indicate better function. (307-309) Minimum clinically important difference (MCID) presents the amount of change resulting in a clinically discernible difference to patients. MCID was defined as 12 points for sexual function, (305, 310) 6 for urinary incontinence, (305, 310) 5 for urinary irritative symptoms, (305, 310) 4 for bowel function, (310) and 4 for hormonal function. (305, 310) The proportions of patients who reported a

decline in each domain which exceeds the MCID was determined and compared between treatment groups at each follow-up interval. The bother items were dichotomised into moderate/big bother, and small/very small/no bother, consistent with cut-off points reported elsewhere. (218, 309, 311, 312) We report specific items from the urinary and sexual domains because of their relevance in daily clinical practice for both patients and their physicians. (303) Urinary continence pad usage was dichotomised into 'no pads per day' and '≥ 1 pad per day'. (309)(16)

Statistical Analysis

Descriptive statistics were used to compare differences in patient demographic characteristics between the treatment groups as well as between patients with and without PROMS data. Differences between continuous variables were compared using Wilcoxon rank-sum tests, and differences between categorical variables were compared using Fisher's exact tests or chi-squared tests, depending on sample size at each follow-up interval. The proportions of patients in each treatment group who reached the MCID in deterioration of EPIC-26 Domain scores were described and compared at each follow-up interval. Mixed effects linear regression was performed for each outcome to compare overall differences between the curves. (313) To accurately measure the association between treatment groups and domain score over time, the models were adjusted for age at diagnosis, comorbidity, NCCN disease risk and baseline EPIC domain score. The correlation of treatment with each adverse event outcome score was presented as a beta coefficient estimate with a 95% confidence interval and a p-value. (314) Statistical significance was set at $p < 0.05$.

Propensity score matching was attempted but was unsuccessful due to inadequate sample sizes remaining at 60 months after matching. (Appendix 1, 2) Subgroup analysis was performed on a cohort of patients treated from 2010 onwards, which indicates the transition towards contemporary techniques with the evolution of Intensity Modulated Radiotherapy and Image Guided Radiotherapy

as well as the adoption of Robotic Laparoscopic-Assisted Prostatectomy in South Australia. (Supplementary Table 1) Additional intra-group comparisons (EBRT before 2010 vs EBRT after 2010 [Supplementary Table 2], RP before 2010 vs RP after 2010 [Supplementary Table 3]) and cross-modality comparisons (Supplementary Table 5) were also performed. Whilst treatment data, including the type of surgery (open retropubic and RALP), was available to the investigators, this has not been included in the subgroup analysis due to the risk of attribution disclosure. The STROBE checklist was followed in reporting this observational study (Appendix 1).

Results

Of the 3,279 eligible patients, 1,103 patients (n=824 RP, n=279 EBRT) had evaluable PROMS data. (Figure 1) Table 1 summarises and compares the demographic patient characteristics of patients treated by RP and EBRT. Patients treated by EBRT had a higher median (IQR) age (74 [69-77] vs 66 [62-70], $p < 0.001$) and were more likely to have high NCCN risk disease (n= 167 [61%] vs n=190 [24%], $p < 0.001$) and to receive ADT (n=105 [38%] vs n= 13 [2%], $p<0.001$). Patients treated with EBRT had shorter median (IQR) length of follow-up (4 [3,6] vs 5 [3,8], $p <0.001$).

Patients who completed PROMs appeared to be significantly different from those who did not complete PROMs. Supplementary Table 1 summaries and compares the demographic characteristics of patients who did and did not complete PROMS. Patients who completed PROMS had fewer GU admissions (157 [9%] vs 439 [16], $p < 0.001$) and GI admissions (64 [4%] vs 247 [9%], $p < 0.001$).

Table 2 and Figure 2 compare EPIC-26 Domain Function Scores between RP and EBRT Cohorts at baseline and follow-up intervals. Similarly, Table 3 and Figure 3 compare moderate/big bother scores between groups. Table 4 summarises and compares the proportion of patients with a MCID in EPIC-26 domain scores at follow-up intervals between treatment groups.

Subgroup analysis determined significant differences between the groups despite contemporary techniques. (Supplementary Table 2) Mean bowel domain scores were worse after EBRT at 12 (75 vs 80, $p<0.05$) and 60 months (75 vs 80, $p<0.05$), including a higher proportion of patients with MCID at 12 months (21% vs 10%, $p=0.008$). (Figure 2, Supplementary Table 3)

Discussion

This is the first prospective population-level study to directly compare EPIC-26 scores amongst a cohort of men with clinically localised prostate cancer treated with contemporary techniques over five years of follow-up. Despite the use of contemporary radiotherapy techniques amongst patients with localised prostate cancer, EBRT after 2010 was associated with significantly worse 12 and 60-month bowel domain scores and higher percentages of MCID at 12 months (21% vs 10%, $p = 0.008$) than RP after 2010. Patients treated with EBRT after 2010 had lower pad use per day at 12,24, and 60 months and better urinary incontinence scores at 60 months (87 vs 89, $p < 0.05$), but there was no statistically significant difference in MCID in either group ($p > 0.05$). However, whilst urinary incontinence scores improved over time in the RP after 2010 group, they progressively deteriorated in the EBRT after 2010 group. Similarly, the proportion of patients requiring daily pads, whilst higher post RP after 2010 ($p < 0.05$), was increasing over time post EBRT after 2010 (Supplementary Table 2).

Whilst several other studies compare EPIC-26 scores amongst men with localised prostate cancer treated with primary EBRT or RP (303, 305, 315-317), these mainly include significantly heterogeneous patient groups, (303, 315) outdated treatment techniques (315, 316) and lack five-year follow-up data. (305, 317). Moreover, there are very few population-based comparative studies of QOL outcomes amongst men with localised prostate cancer treated with primary EBRT or RP (175, 304, 305), of which many include heterogenous treatment groups (e.g. primary and salvage, EBRT + Brachytherapy), (175, 304) non-validated PROM instruments, (175, 304) or lack five-year outcomes. (305) Furthermore, of the two RCTs comparing PROMS amongst men with localised prostate cancer treated with primary EBRT or RP, (301, 302) neither includes five-year PROMS. The phase 3 non-inferiority CCHip Trial compared men treated with normofractionated (74Gy/37# [n= 696]) vs hypofractionated (60Gy/20# [n=698], 57Gy/19# [n=706]) EBRT and limited to 24-month outcome data. (301)

Despite bowel domain scores being significantly better at baseline in the EBRT group, bowel scores remained significantly worse until the 60-month follow-up (beta -0.46, 95% CI -1.20 - 0.28, p<0.001). In addition, a higher proportion of patients with MCID in bowel domain score was identified at 12 months (22 vs 11%, p=0.009; Table 2; Figure 2) in the EBRT than the RP group. In addition, the proportion of patients with moderate/big bowel bother scores were significantly higher in the EBRT cohort at baseline and all follow-up periods (beta -8.27, 95% CI -10.21 - -6.34, p<0.001; Table 2, Figure 3). Several other studies have similarly demonstrated worse bowel function associated with EBRT compared to radical prostatectomy; however, these mainly involve outdated radiotherapy techniques. (302, 315, 318) Donovan et al. analysed PROMS from the PROTECT trial (n=1643) and determined worse bowel function amongst patients with localised prostate cancer six months after treatment with EBRT (3D-CRT, 74Gy/37#) compared to prostatectomy or active surveillance. (302) Other studies support our finding of bowel dysfunction persisting beyond 12 months post-treatment. (315, 318) Yagi et al., in a single institution study involving men with localised prostate cancer without ADT (RRP n= 101 vs EBRT n=23), determined that 3-year EPIC-26 bowel function and bother scores were significantly worse after EBRT. (318) Similarly, a conference article by Zhou et al. compared men with localised prostate cancer treated between 1955-1999 and found that treatment with RP was associated with better bowel function at 15-year follow-up. (315) However, this study was limited by significant differences between patient groups (age, comorbidity, baseline quality of life), the single institution design and the use of outdated treatment techniques.

EBRT was associated with less pad use at 12 (4% vs 34%, p <0.001), 24 (10% vs 33%, p <0.001) and 60 months (13% vs 33%, p = 0.15) than RP (Table 3). The systematic review by Baker et al. supported our findings that urinary incontinence, whilst initially worse after RP, improves over time but gradually deteriorates following EBRT. (154) A more recent cross-sectional study of men with low-risk prostate cancer (n=219, RT vs n=69, RP vs n=120, AS) by Venderbos et al. similarly found that the RT group

reported less mean (SD) urinary incontinence (86.5 [20.3] vs. 70.1 [28.8]) and fewer pads per day (8% vs 38%). (303) However, this study only involved a heterogenous RT group (BT, EBRT, BT+EBRT) and a less rigorous one-time QoL questionnaire. Whilst the current study determines a lower proportion of patients with MCID in urinary incontinence domain score at 60 months in the EBRT than the RP cohort, this is limited by small sample sizes in the former group (4 / 38 [11%] vs 57 / 226 [25%] vs, p=0.047**,** Table 4).

We found that mean urinary irritative/obstructive domain scores were similar at baseline but significantly worse in the EBRT group over time (beta=-1.82, 95% CI -3.13 - -0.52, p<0.001; Figure 2); however, there was no statistically significant difference in MCID (Table 2). These findings are supported by the single-centre cross-sectional study by Zhou et al. (315), which compared RP and 3DCRT without IGRT (1995-1999) and reported worse EPIC-26 Urinary Irritative/ Obstructive Domain scores in the EBRT group.

We found that the mean percentage of moderate/big urinary bother was higher amongst the EBRT group at baseline and at 12 and 24-month follow-up intervals. The mean percentage of Moderate/big urinary bother was lower at 60-month interval follow-up following EBRT (beta -4.75, 95% CI -7.26 - -2.24, p<0.001; Figure 3); however, this may be due to the low sample sizes remaining at 60 months with evaluable data (n= 363, RP vs n = 38, EBRT). The impact of EBRT on late patient-reported urinary toxicity far exceeds that reported by the recent ProtecT trial, which reported that urinary voiding and dysuria were similar between groups at 12 months. (302) The differences may be related to the increased mean (sd) age in our study compared to the ProtecT trial (73 [7] vs 62 [5]) as well as higher proportions of patients with higher-risk disease.

We found that mean sexual domain scores were also lower (i.e. worse) in the EBRT group (beta= -4.57, 95% CI -8.04 - -1.11, p<0.001; Figure 2), with significant differences between groups in the proportions who reached MCID at 24 (2 vs 14%, p=0.017) and 60-month (0 vs 12%, p=0.019) intervals (Table 2). However, there were no significant differences in sexual bother scores reported during follow-up (Table 3, Figure 3). Many studies have reported more significant decreases in sexual function following RP compared to EBRT. (315, 318, 319) These studies include randomised controlled trials, (302) population level (29) and prospective multi-institution (316) studies. However, these studies often used outdated techniques (315, 316) that did not report EPIC-26 (19, 29), did not include five-year outcome data (303, 315, 318) or adjusted for significant differences in baseline characteristics between the groups. (303, 315, 316, 318) Yagi et al. supported our finding that sexual function scores in the EBRT group progressively deteriorated over time, whereas the RP group gradually improved over time. (318)

Patients treated with EBRT had significantly lower (i.e. worse) median hormonal domain scores at baseline (90 vs 95, p<0.001) and at all follow-up periods (beta= -2.20, 95% CI -3.37 - -1.03, p<0.001); Table 2; Figure 2). However, there were no significant differences in the proportion of patients within each group who reached MCID in hormonal domain scores at each interval (p > 0.05). Yagi et al. also found that both groups' EPIC-26 hormonal function and bother scores remained similar. (318) However, neither group received ADT, and the generalisability of the findings is limited by the single institution only. (318)

This study has several limitations. Firstly, there were significant differences in the baseline characteristics between groups; however, age, comorbidity, NCCN disease risk and baseline EPIC-26 scores were adjusted for in multivariable regression. ADT use was not controlled for in the model because concurrent ADT forms part of standard radiotherapy treatment for patients with intermediate and high-risk prostate cancer. (320) Secondly, the definition of MCID may differ in the literature and

between patients. Moreover, the aggregation of data from an observational cohort may fail to accurately describe the adverse events for individuals, such as personalised risk estimates. However, our use of a multivariable mixed effects linear regression model aims to provide a reasonable estimate of adverse events experienced by individuals over repeated measures. Thirdly, there were low sample sizes remaining at 60 months, particularly amongst the EBRT group (n=38), which will affect the accuracy of findings. However, the potential bias from missing data and group imbalance has been mitigated by the use of a linear mixed-effects model. (313) Finally, the study relies on the EPIC-26 score, which does not include measures of patient mood, satisfaction or cost analysis.(321) An improved understanding of the toxicity profile and patterns associated with these contemporary treatment options for localised prostate cancer could inform shared decision-making between patients and their clinicians in the pre-treatment counselling setting.

Author Declarations

Competing Interests

The authors have no competing interests to declare that are relevant to the content of this article.

Ethics Approval

The SA-PCCOC database has been approved by the Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC). Approval to access the database was granted by the SA-PCCOC steering committee. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Author Contributions

RV David: project development, data collection, data analysis and manuscript writing.

AA Kahokehr: data analysis and manuscript editing.

J Lee: project development and manuscript editing.

J Leung: data analysis and manuscript editing.

DI Watson: project development and manuscript editing.

ME O'Callaghan: project development, data analysis and manuscript editing.

All authors have read and approved the final manuscript.

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Figures

Figure 1. Flow Chart of Patient Selection Process

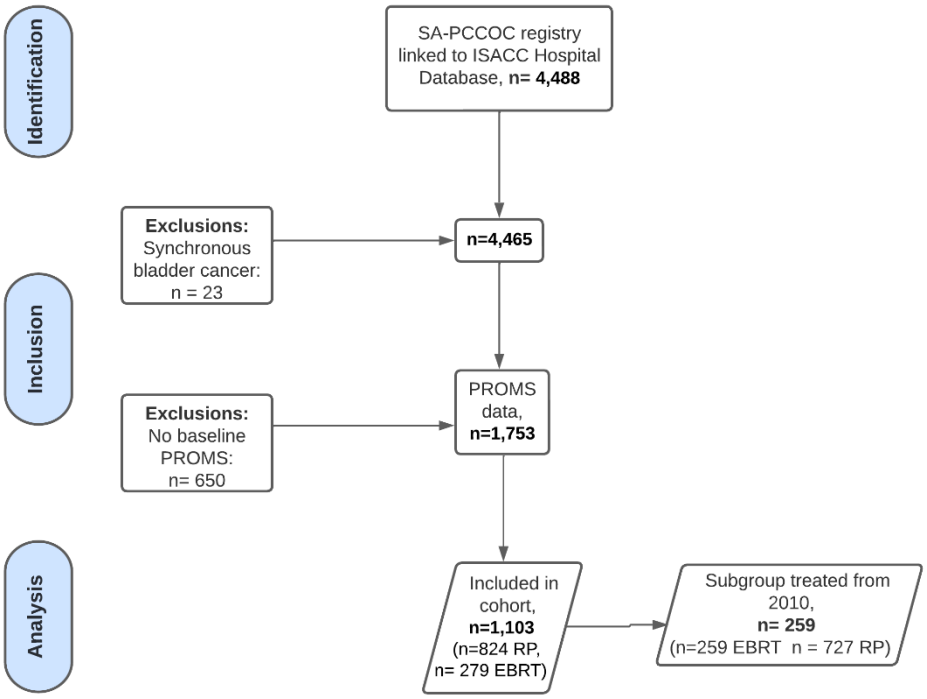


Figure 2. Comparison of Mean EPIC-26 Domain Scores Between EBRT and RP Cohorts

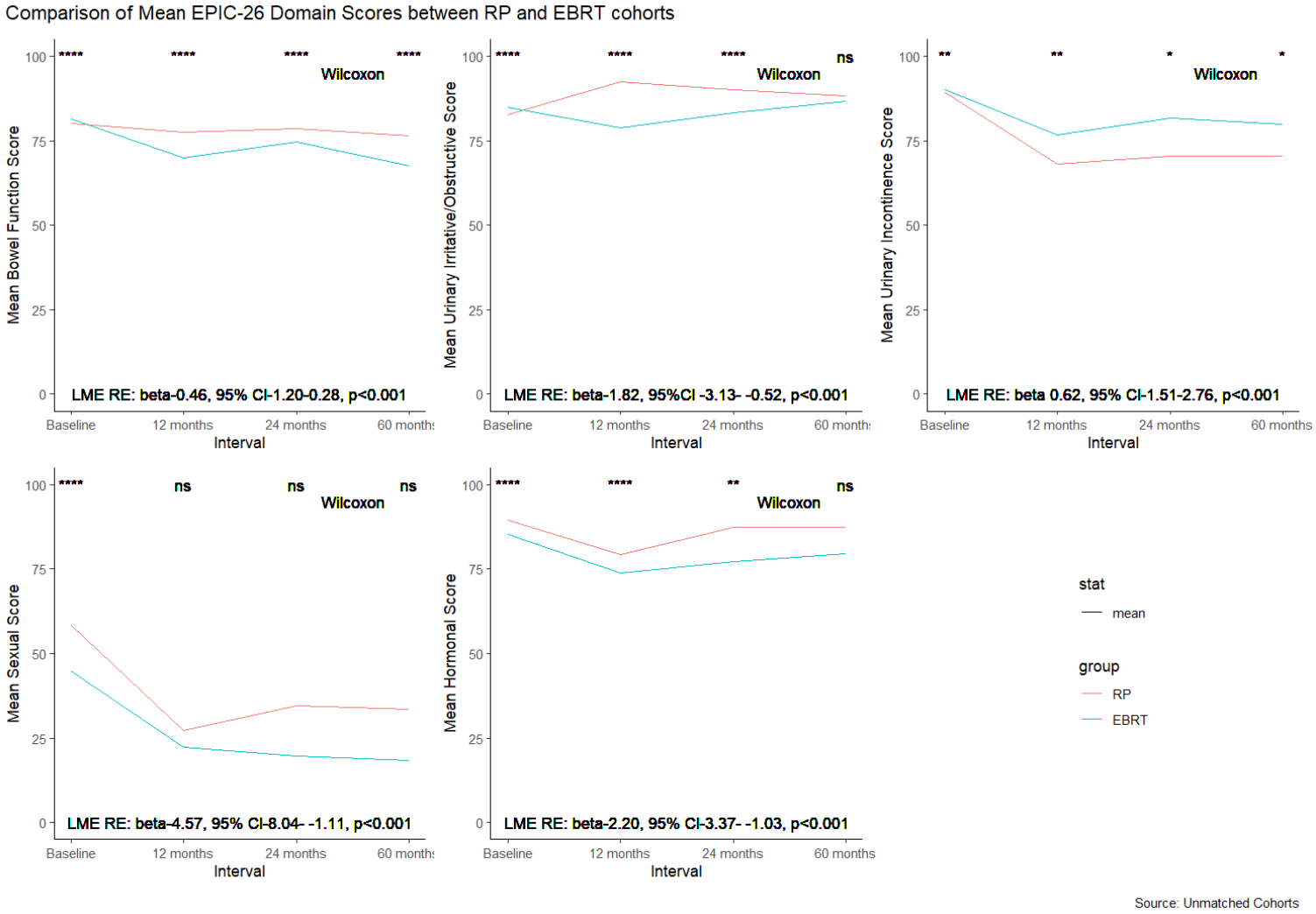
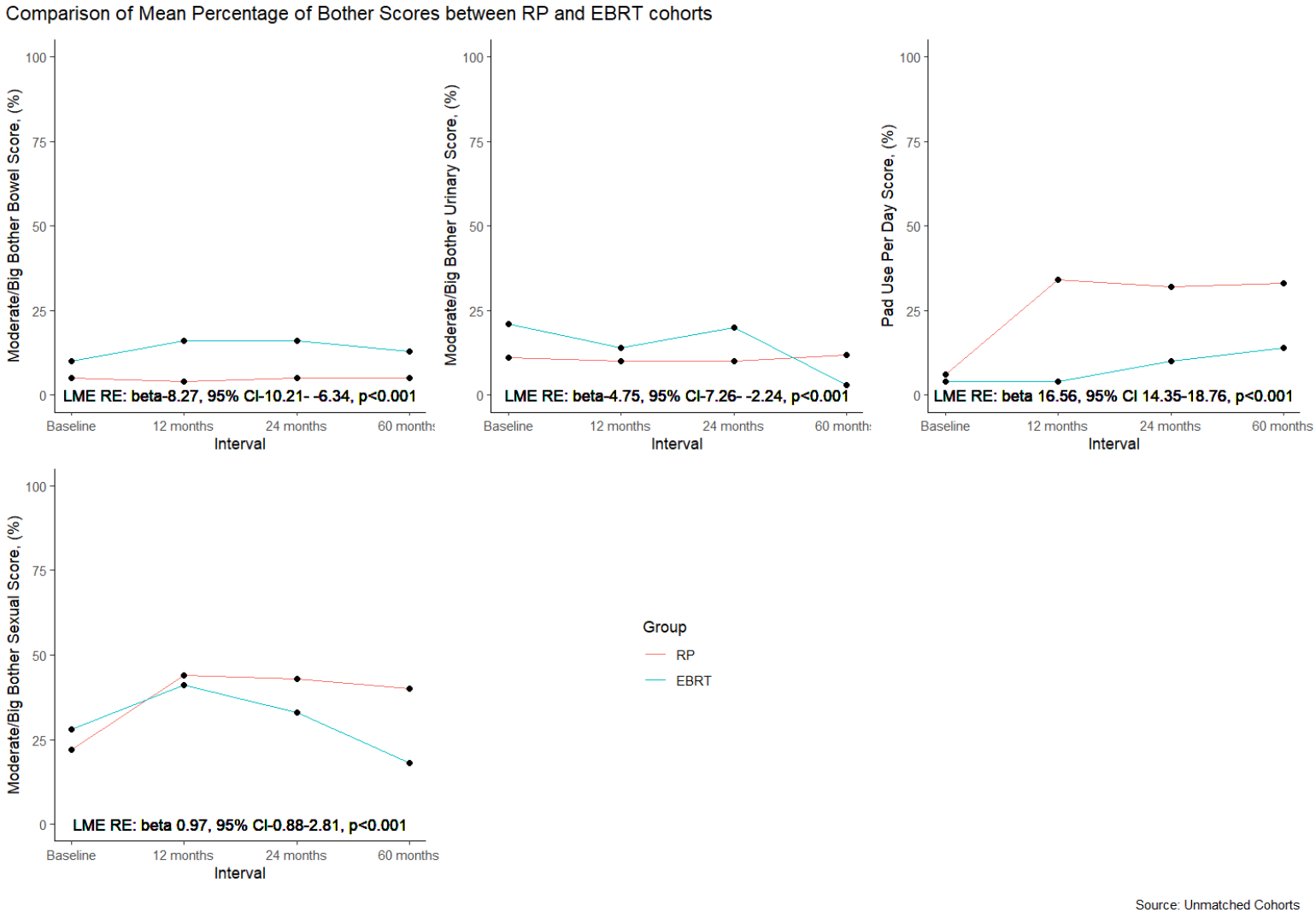


Figure 3. Comparison of Mean EPIC-26 Moderate/Big Bother Scores Between EBRT and RP Cohorts



Source: Unmatched Cohorts

Tables

Table 1. Comparison of Demographic Characteristics of Included Patients with Evaluable PROMS

		Treatment modality		
Characteristic	Overall, N = 1,103[1]	RP, N = 824[1]	EBRT, N = 279[1]	p-value[2]
Age at diagnosis	68 (63, 72)[1]	66 (62, 70)[1]	74 (69, 77)[1]	<0.001[2]
Charlson Score	0 (0, 1)	0 (0, 1)	1 (0, 2)	<0.001[3]
NCCN Risk Category				<0.00[3]
High	357 (33%)	190 (24%)	167 (61%)	
Intermediate	482 (45%)	407 (51%)	75 (27%)	
Low	232 (22%)	201 (25%)	31 (11%)	
(Missing)	32	26	6	
iPSA Level				<0.001[3]
1.<4	90 (9%)	77 (10%)	13 (5%)	
2.4-10	660 (65%)	544 (72%)	116 (45%)	
3.>10	264 (26%)	136 (18%)	128 (50%)	
(Missing)	89	67	22	
ISUP Grade				<0.001[3]
1.1	311 (28%)	264 (32%)	47 (17%)	

		Treatment modality		
Characteristic	Overall, N = 1,103[1]	RP, N = 824[1]	EBRT, N = 279[1]	p-value[2]
2.2	366 (34%)	305 (37%)	61 (22%)	
3.3	196 (18%)	136 (17%)	60 (22%)	
4.>3	219 (20%)	109 (13%)	110 (40%)	
(Missing)	11	10	1	
ADT	118 (11%)	13 (2%)	105 (38%)	<0.001[3]
Operation type				
Open	115 (14%)	115 (14%)	0 (NA%)	
RALP	703 (86%)	703 (86%)	0 (NA%)	
(Missing)	285	6	279	
Dose Gy	78 (74, 78)[1]	NA (NA, NA)	78 (74, 78)[1]	
(Missing)	832	824	8	
Fractions	39 (37, 39)[1]	NA (NA, NA)	39 (37, 39)[1]	
(Missing)	832	824	8	
Treatment Date				<0.00[3]
1. <2010	108 (10%)	97 (12%)	11 (4%)	
2. ≥2010	995 (90%)	727 (88%)	268 (96%)	

		Treatment modality		
Characteristic	Overall, N = 1,103[1]	RP, N = 824[1]	EBRT, N = 279[1]	p-value[2]
Follow up years	5 (3, 7)[1]	5 (3, 8)[1]	4 (3, 6)[1]	<0.001[2]

[1]n (%); Median (IQR)

[2]Wilcoxon rank sum test; [3]Pearson's Chi-squared test

Table 2. Comparison of EPIC-26 Domain Scores Amongst Patients with Evaluable PROMS

	Baseline				12 Months				24 Months				60 Months			
Characteristic	Overall, N = 1,103[1]	RP, N = 824[1]	EBRT, N = 279[1]	p-value[2]	Overall, N = 516[1]	RP, N = 439[1]	EBRT, N = 77[1]	p-value[2]	Overall, N = 311[1]	RP, N = 259[1]	EBRT, N = 52[1]	p-value[2]	Overall, N = 264[1]	RP, N = 226[1]	EBRT, N = 38[1]	p-value[2]
Bowel	81 (7)	81 (7)	80 (9)	0.7	80 (8)	81 (6)	73 (14)	<0.001	79 (8)	80 (7)	76 (12)	0.002	78 (10)	79 (9)	73 (15)	0.004
(Missing)	68	46	22		21	18	3		12	9	3		13	9	4	
Urinary Irritative/Obstructive	84 (16)	86 (15)	80 (17)	<0.001	91 (11)	92 (10)	82 (16)	<0.001	90 (12)	91 (12)	84 (14)	<0.001	90 (13)	90 (13)	89 (12)	0.49
(Missing)	93	54	39		37	25	12		18	11	7		25	21	4	
Urinary Incontinence	89 (18)	89 (18)	87 (17)	0.005	74 (23)	73 (23)	83 (20)	<0.001	75 (23)	74 (24)	81 (22)	0.016	74 (25)	72 (26)	84 (17)	0.012
(Missing)	87	52	35		37	26	11		28	24	4		21	18	3	
Hormonal	90 (13)	91 (12)	86 (15)	<0.001	88 (14)	90 (12)	78 (19)	<0.001	89 (15)	90 (13)	80 (23)	0.022	88 (15)	89 (15)	85 (17)	0.22
(Missing)	141	86	55		44	34	10		32	23	9		27	22	5	
Sexual	58 (30)	62 (29)	41 (27)	<0.001	33 (27)	34 (27)	24 (19)	0.057	36 (30)	38 (30)	22 (16)	0.071	37 (28)	39 (29)	21 (12)	0.043

	Baseline				12 Months				24 Months				60 Months			
Characteristic	Overall, N = 1,103[1]	RP, N = 824[1]	EBRT, N = 279[1]	p-value[2]	Overall, N = 516[1]	RP, N = 439[1]	EBRT, N = 77[1]	p-value[2]	Overall, N = 311[1]	RP, N = 259[1]	EBRT, N = 52[1]	p-value[2]	Overall, N = 264[1]	RP, N = 226[1]	EBRT, N = 38[1]	p-value[2]
(Missing)	299	175	124		178	137	41		106	79	27		99	78	21	

[1]Mean (SD)

[2]Wilcoxon rank sum test

Table 3. Comparison of EPIC-26 Bother Scores Amongst Patients with Evaluable PROMS

	Baseline				12 Months				24 Months				60 Months			
Characteristic	Overall, N = 1,103[1]	RP, N = 824[1]	NEBRT, N = 279[1]	p-value[2]	Overall, N = 516[1]	RP, N = 439[1]	NEBRT, N = 77[1]	p-value[3]	Overall, N = 311[1]	RP, N = 259[1]	NEBRT, N = 52[1]	p-value[3]	Overall, N = 264[1]	RP, N = 226[1]	NEBRT, N = 38[1]	p-value[3]
Bowel Bother	64 (6%)	38 (5%)	26 (10%)	0.003	29 (6%)	17 (4%)	12 (16%)	<0.001	21 (7%)	13 (5%)	8 / 51 (16%)	0.012	18 (7%)	13 (6%)	5 / 38 (13%)	0.2
	1,086	813	273		511	435	76		307	256			263	225		
(Missing)	17	11	6		5	4	1		4	3	1		1	1	0	
Urinary Bother	147 (14%)	92 (11%)	55 (21%)	<0.001	54 (11%)	43 (10%)	11 (14%)	0.3	37 (12%)	26 (10%)	11 (21%)	0.025	29 (11%)	28 (12%)	1 / 38 (3%)	0.092
	1,074	806	268		505	428	77		309	257	52		262	224		
(Missing)	29	18	11		11	11	0		2	2	0		2	2	0	
Pads per day	63 (6%)	51 (6%)	12 (5%)	0.3	149 (30%)	146 (34%)	3 / 75 (4%)	<0.001	84 (29%)	79 (33%)	5 / 51 (10%)	<0.001	77 (30%)	72 (33%)	5 / 38 (13%)	0.015
	1,069	804	265		500	425			292	241			258	220		
(Missing)	34	20	14		16	14	2		19	18	1		6	6	0	
Sexual Bother	211 (23%)	156 (22%)	55 (28%)	0.063	179 (44%)	156 (44%)	23 (43%)	0.8	107 (43%)	94 (44%)	13 (39%)	0.7	79 (38%)	71 (39%)	8 / 28 (29%)	0.3
	904	710	194		405	351	54		249	216	33		210	182		
(Missing)	199	114	85		111	88	23		62	43	19		54	44	10	

	Baseline				12 Months				24 Months				60 Months			
Characteristic	Overall, N = 1,103[1]	RP, N = 824[1]	NEBRT, N = 279[1]	p-value[2]	Overall, N = 516[1]	RP, N = 439[1]	NEBRT, N = 77[1]	p-value[3]	Overall, N = 311[1]	RP, N = 259[1]	NEBRT, N = 52[1]	p-value[3]	Overall, N = 264[1]	RP, N = 226[1]	NEBRT, N = 38[1]	p-value[3]
Haematuria	16 (2%)	10 (1%)	6 (2%)	0.2	1 / 487 (0%)	1 / 420 (0%)	0 / 67 (0%)	>0.9	1 / 298 (0%)	1 / 251 (0%)	0 / 47 (0%)	>0.9	3 / 243 (1%)	3 / 207 (1%)	0 / 36 (0%)	>0.9
Bother	1,029 (93%)	782 (95%)	247 (89%)		487 (94%)	420 (96%)	67 (87%)		298 (96%)	251 (97%)	47 (90%)		243 (92%)	207 (92%)	36 (95%)	
(Missing)	74	42	32		29	19	10		13	8	5		21	19	2	

[1]n / N (%)

[2]Pearson's Chi-squared test; [3]Pearson's Chi-squared test; [4]Fisher's exact test

Table 4. Comparison of MCID Amongst Patients with Evaluable PROMS

	12 Months			24 Months			60 Months		
Characteristic	Overall, N = 516[1]	RP, N = 439[1]	EBRT, N = 77[1]	p-value[2]	Overall, N = 311[1]	RP, N = 259[1]	EBRT, N = 52[1]	p-value[2]	Overall, N = 264[1]	RP, N = 226[1]	EBRT, N = 38[1]	p-value[3]
Hormonal change	63 / 516 (12%)	52 / 439 (12%)	11 / 77 (14%)	0.5	56 / 311 (18%)	49 / 259 (19%)	7 / 52 (13%)	0.35	54 / 264 (20%)	48 / 226 (21%)	6 / 38 (16%)	0.44
Bowel Change	61 / 516 (12%)	41 / 439 (9%)	20 / 77 (26%)	<0.001	50 / 311 (16%)	39 / 259 (15%)	11 / 52 (21%)	0.27	48 / 264 (18%)	35 / 226 (15%)	13 / 38 (34%)	0.006
UO Change	82 / 516 (16%)	65 / 439 (15%)	17 / 77 (22%)	0.1	57 / 311 (18%)	46 / 259 (18%)	11 / 52 (21%)	0.56	46 / 264 (17%)	35 / 226 (15%)	11 / 38 (29%)	0.043
UI Change	105 / 516 (20%)	94 / 439 (21%)	11 / 77 (14%)	0.2	73 / 311 (23%)	66 / 259 (25%)	7 / 52 (13%)	0.062	61 / 264 (23%)	57 / 226 (25%)	4 / 38 (11%)	0.047
Sexual Change	40 / 516 (8%)	36 / 439 (8%)	4 / 77 (5%)	0.4	44 / 311 (14%)	41 / 259 (16%)	3 / 52 (6%)	0.057	32 / 264 (12%)	31 / 226 (14%)	1 / 38 (3%)	0.059

[1]n / N (%)

	12 Months			24 Months			60 Months		
Characteristic	Overall, N = 516[1]	RP, N = 439[1]	EBRT, N = 77[1]	p-value[2]	Overall, N = 311[1]	RP, N = 259[1]	EBRT, N = 52[1]	p-value[2]	Overall, N = 264[1]	RP, N = 226[1]	EBRT, N = 38[1]	p-value[3]

[2]Pearson's Chi-squared test

[3]Pearson's Chi-squared test; Fisher's exact test

Supplementary Tables

Supplementary Table 1: Comparison of Patients with PROMs vs No PROMS

		PROMS completed		
Characteristic	Overall, N = 4,465[1]	No, N = 2,712[1]	Yes, N = 1,753[1]	p-value
Age at diagnosis	68 (63, 73)[1]	68 (63, 74)[1]	68 (63, 72)[1]	<0.001[2]
(Missing)	1	1	0	
Charlson Score	1 (0, 2)	1 (0, 2)	0 (0, 1)	<0.0012[3]
(Missing)	1	1	0	
NCCN Risk Category				<0.001[3]
High	1,596 (38%)	1,023 (41%)	573 (34%)	
Intermediate	1,718 (41%)	953 (38%)	765 (45%)	
Low	889 (21%)	532 (21%)	357 (21%)	
(Missing)	262	204	58	
iPSA Level				<0.001[3]
1.<4	300 (8%)	148 (6%)	152 (10%)	
2.4-10	2,201 (56%)	1,188 (51%)	1,013 (64%)	
3.>10	1,395 (36%)	974 (42%)	421 (27%)	
(Missing)	569	402	167	

		PROMS completed		
Characteristic	Overall, N = 4,465[1]	No, N = 2,712[1]	Yes, N = 1,753[1]	p-value
ISUP Grade				<0.001[3]
1.1	1,522 (35%)	1,037 (40%)	485 (28%)	
2.2	1,262 (29%)	669 (26%)	593 (34%)	
3.3	709 (16%)	402 (15%)	307 (18%)	
4.>3	836 (19%)	499 (19%)	337 (20%)	
(Missing)	136	105	31	
ADT	1,084 (24%)	845 (31%)	239 (14%)	<0.001[3]
(Missing)	1	1	0	
EBRT	2,359 (53%)	1,869 (69%)	490 (28%)	<0.001[3]
(Missing)	1	1	0	
Treatment Date				<0.001[3]
1. <2010	1,730 (39%)	1,484 (55%)	246 (14%)	
2. ≥2010	2,712 (61%)	1,206 (45%)	1,506 (86%)	
(Missing)	23	22	1	
Dose Gy	74 (70, 78)[1]	74 (70, 74)[1]	78 (74, 78)[1]	<0.001[2]
(Missing)	2,295	1,010	1,285	

		PROMS completed		
Characteristic	Overall, N = 4,465[1]	No, N = 2,712[1]	Yes, N = 1,753[1]	p-value
Fractions	37 (35, 39)[1]	37 (35, 37)[1]	39 (37, 39)[1]	<0.001[2]
(Missing)	2,297	1,011	1,286	
Follow up, years	7 (4, 11)[1]	9 (5, 13)[1]	6 (4, 8)[1]	<0.001[2]
Any Admission	4,464 (100%)	2,711 (100%)	1,753 (100%)	
Any Recurrent Admissions	3 (1, 7)	2 (1, 7)[1]	3 (1, 7)[1]	<0.001[2]
GU Admission	596 (13%)	439 (16%)	157 (9%)	<0.001[3]
GU Recurrent Admissions	1 (0, 2)	0 (0, 2)[1]	1 (0, 3)[1]	<0.001[2]
GI Admission	311 (7%)	247 (9%)	64 (4%)	<0.001[3]
Haematuria Admission	299 (7%)	227 (8%)	72 (4%)	<0.001[3]
Haematuria Recurrent Admission	0 (0, 1)	0 (0, 1)[1]	1 (0, 3)[1]	<0.001[2]
Proctitis Admission	299 (7%)	238 (9%)	61 (3%)	<0.001[3]

[1]n (%); Median (IQR)

[2]Wilcoxon rank sum test; [3]Pearson's Chi-squared test

Supplementary Table 2. Subgroup Analysis of Patients Treatment Using Contemporary Techniques (RP VS EBRT ≥ 2010)

	Baseline				12 Months				24 Months				60 Months			
Characteristic	Overall, N = 986[1]	RP, N = 727[1]	EBRT, N = 259[1]	p-value[2]	Overall, N = 986[1]	NRP, N = 727[1]	EBRT, N = 259[1]	p-value[2]	Overall, N = 986[1]	NRP, N = 727[1]	EBRT, N = 259[1]	p-value[2]	Overall, N = 986[1]	NRP, N = 727[1]	EBRT, N = 259[1]	p-value[3]
Bowel Score	80 (8)	80 (7)	79 (10)	0.51	80 (8)	80 (7)	75 (14)	0.007	79 (9)	80 (7)	76 (14)	0.066	80 (9)	80 (8)	75 (14)	0.040
(Missing)	61	43	18		549	359	190		710	495	215		750	527	223	
Bowel Bother	56 / 97031 (6%)	717 (4%)	/25 / 2530.001 (10%)		25 / 45214 (6%)	381 (4%)	/11 / 71<0.001 (15%)		21 / 28612 (7%)	238 (5%)	/9 / 48<0.001 (19%)		18 / 24613 (7%)	208 (6%)	/5 / 380.17 (13%)	
(Missing)	16	10	6		534	346	188		700	489	211		740	519	221	
UO Score	86 (16)	88 (15)	82 (17)	<0.001	88 (13)	90 (12)	80 (17)	<0.001	88 (13)	89 (13)	83 (15)	0.002	89 (14)	89 (13)	86 (16)	0.20
(Missing)	97	57	40		559	363	196		716	499	217		756	531	225	

	Baseline				12 Months				24 Months				60 Months			
Characteristic	Overall, N = 986[1]	RP, N = 727[1]	EBRT, N = 259[1]	p-value[2]	Overall, N = 986[1]	NRP, N = 727[1]	EBRT, N = 259[1]	p-value[2]	Overall, N = 986[1]	NRP, N = 727[1]	EBRT, N = 259[1]	p-value[2]	Overall, N = 986[1]	NRP, N = 727[1]	EBRT, N = 259[1]	p-value[3]
UI Score	83 (23)	82 (24)	85 (19)	0.38	81 (23)	80 (24)	83 (20)	0.64	79 (23)	79 (23)	82 (20)	0.45	79 (23)	78 (24)	87 (16)	0.047
(Missing)	94	59	35		554	362	192		723	508	215		751	526	225	
Pads per day	54 / 95 (6%)	44 / 70 (6%)	10 / 24 (4%)	0.22	131 / 441 (30%)	128 / 371 (35%)	3 / 70 (4%)	<0.001	78 / 271 (29%)	73 / 223 (33%)	5 / 48 (10%)	0.002	71 / 241 (29%)	66 / 203 (33%)	5 / 38 (13%)	0.016
(Missing)	33	18	15		545	356	189		715	504	211		745	524	221	
Urinary Bother	124 / 960 (13%)	76 / 712 (11%)	48 / 248 (19%)	<0.001	44 / 447 (10%)	36 / 375 (10%)	8 / 72 (11%)	0.69	34 / 288 (12%)	24 / 239 (10%)	10 / 49 (20%)	0.040	26 / 246 (11%)	25 / 208 (12%)	1 / 38 (3%)	0.083
(Missing)	26	15	11		539	352	187		698	488	210		740	519	221	

	Baseline				12 Months				24 Months				60 Months			
Characteristic	Overall, N = 986[1]	RP, N = 727[1]	EBRT, N = 259[1]	p-value[2]	Overall, N = 986[1]	NRP, N = 727[1]	EBRT, N = 259[1]	p-value[2]	Overall, N = 986[1]	NRP, N = 727[1]	EBRT, N = 259[1]	p-value[2]	Overall, N = 986[1]	NRP, N = 727[1]	EBRT, N = 259[1]	p-value[3]
Hormonal Score	89 (14)	90 (13)	85 (15)	<0.001	89 (13)	90 (12)	82 (17)	<0.001	89 (14)	90 (12)	84 (20)	0.14	90 (13)	90 (12)	90 (15)	0.60
(Missing)	134	78	56		569	372	197		723	505	218		760	534	226	
Sexual Score	47 (33)	50 (33)	34 (28)	<0.001	41 (32)	42 (32)	31 (28)	0.027	40 (32)	41 (32)	28 (27)	0.045	40 (32)	41 (32)	28 (25)	0.066
(Missing)	273	159	114		637	420	217		770	538	232		800	567	233	
Sexual Bother	192 / 816 (24%)	142 / 633 (22%)	50 / 183 (27%)	0.17	159 / 367 (43%)	137 / 316 (43%)	22 / 51 (43%)	0.98	100 / 234 (43%)	88 / 204 (43%)	12 / 30 (40%)	0.75	72 / 196 (37%)	64 / 168 (38%)	8 / 28 (29%)	0.33
(Missing)	170	94	76		619	411	208		752	523	229		790	559	231	

	Baseline				12 Months				24 Months				60 Months			
Characteristic	Overall, N = 986[1]	RP, N = 727[1]	EBRT, N = 259[1]	p-value[2]	Overall, N = 986[1]	NRP, N = 727[1]	EBRT, N = 259[1]	p-value[2]	Overall, N = 986[1]	NRP, N = 727[1]	EBRT, N = 259[1]	p-value[2]	Overall, N = 986[1]	NRP, N = 727[1]	EBRT, N = 259[1]	p-value[3]
Bowel Change					55 / 457 (12%)	42 / 385 (11%)	13 / 72 (18%)	0.087	39 / 290 (13%)	27 / 241 (11%)	12 / 49 (24%)	0.013	35 / 247 (14%)	27 / 209 (13%)	8 / 38 (21%)	0.19
(Missing)					529	342	187		696	486	210		739	518	221	
UO change					84 / 457 (18%)	67 / 385 (17%)	17 / 72 (24%)	0.21	66 / 290 (23%)	54 / 241 (22%)	12 / 49 (24%)	0.75	49 / 247 (20%)	42 / 209 (20%)	7 / 38 (18%)	0.81
(Missing)					529	342	187		696	486	210		739	518	221	
UI change					67 / 457 (15%)	56 / 385 (15%)	11 / 72 (15%)	0.87	62 / 290 (21%)	50 / 241 (21%)	12 / 49 (24%)	0.56	50 / 247 (20%)	46 / 209 (22%)	4 / 38 (11%)	0.11

	Baseline				12 Months				24 Months				60 Months			
Characteristic	Overall, N = 986[1]	RP, N = 727[1]	EBRT, N = 259[1]	p-value[2]	Overall, N = 986[1]	NRP, N = 727[1]	EBRT, N = 259[1]	p-value[2]	Overall, N = 986[1]	NRP, N = 727[1]	EBRT, N = 259[1]	p-value[2]	Overall, N = 986[1]	NRP, N = 727[1]	EBRT, N = 259[1]	p-value[3]
(Missing)					529	342	187		696	486	210		739	518	221	
Hormonal change					52 / 457 (11%)	43 / 385 (11%)	9 / 72 (12%)	0.74	58 / 290 (20%)	50 / 241 (21%)	8 / 49 (16%)	0.48	48 / 247 (19%)	43 / 209 (21%)	5 / 38 (13%)	0.29
(Missing)					529	342	187		696	486	210		739	518	221	
Sexual Change					56 / 457 (12%)	52 / 385 (14%)	4 / 72 (6%)	0.059	44 / 290 (15%)	41 / 241 (17%)	3 / 49 (6%)	0.053	31 / 247 (13%)	28 / 209 (13%)	3 / 38 (8%)	0.35
(Missing)					529	342	187		696	486	210		739	518	221	

[1]Mean (SD); n / N (%)

	Baseline				12 Months				24 Months				60 Months			
Characteristic	Overall, N = 986[1]	RP, N = 727[1]	EBRT, N = 259[1]	p-value[2]	Overall, N = 986[1]	NRP, N = 727[1]	EBRT, N = 259[1]	p-value[2]	Overall, N = 986[1]	NRP, N = 727[1]	EBRT, N = 259[1]	p-value[2]	Overall, N = 986[1]	NRP, N = 727[1]	EBRT, N = 259[1]	p-value[3]

[2]Wilcoxon rank sum test; Pearson's Chi-squared test

[3]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Supplementary Table 3. Mixed Effects Linear Regression of Relationship between EBRT and EPIC-26 scores with Adjustment for Age, Comorbidity, NCCN risk and Baseline score

Outcome/ Covariable	Beta Coefficient	95% CI	P value
Bowel Domain Score			
EBRT	-0.46	-1.20 - 0.28	p<0.001
Age	-0.03	-0.07 - 0.01	p=0.096
Charlson Score	-0.12	-0.33 - 0.09	p=0.127
NCCN	-0.03	-0.42 - 0.35	p=0.433
Baseline Score	0.72	0.68 - 0.75	p<0.001
Interval	-0.75	-0.99 - -0.52	p<0.001
Urinary Irritative/Obstructive Domain Score			
EBRT	-1.82	-3.13 - -0.52	p<0.001
Age	-0.01	-0.08 - 0.06	p<0.001
Charlson Score	-0.17	-0.54 - 0.20	p<0.001
NCCN	-0.34	-1.00-0.33	p<0.001
Baseline Score	0.69	0.66-0.72	p<0.001
Interval	1.24	0.82-1.66	p<0.001
Urinary Incontinence Domain Score			
EBRT	0.62	-1.51 - 2.76	p<0.001
Age	-0.12	-0.24 - 0.00	p<0.001
Charlson Score	-0.10	-0.70 - 0.50	p<0.001
NCCN	-0.02	-1.11 - 1.06	p<0.001

Baseline Score	0.64	0.61 - 0.68	p<0.001
Interval	-4.67	-5.36 - -3.99	p<0.001
Sexual Domain Score			
EBRT	-4.57	-8.04 - -1.11	p<0.001
Age	-0.34	-0.53 - -0.15	p<0.001
Charlson Score	-0.37	-1.41 - 0.67	p<0.001
NCCN	-0.77	-2.46 - 0.93	p<0.001
Baseline Score	0.64	0.64 - 0.71	p<0.001
Interval	-7.89	-8.89 - -6.89	p<0.001
Hormonal Domain Score			
EBRT	-2.20	-3.37 - -1.03	p<0.001
Age	0.03	-0.03 - 0.10	p<0.001
Charlson Score	-0.09	-0.42 - 0.24	p<0.001
NCCN	-0.45	-1.04 - 0.13	p<0.001
Baseline Score	0.64	0.74 - 0.80	p<0.001
Interval	0.77	-1.07 - -0.35	p<0.001
Moderate/Big Bother Bowel Score			
EBRT	-8.27	-10.21 - -6.34	p<0.001
Age	-0.05	-0.16 - 0.07,	p<0.001
Charlson Score	-0.52	-1.07 - 0.03	p<0.001
NCCN	-0.56	-1.58 - 0.47	p<0.001
Baseline Score	-56.87	-59.85 - -53.89	p<0.001
Interval	-0.57	-1.20 - 0.05	p<0.001

Moderate/Big Bother Urinary Score			
EBRT	-4.75	-7.26 - -2.24	p<0.001
Age	-0.04	-0.19 - 0.10	p<0.001
Charlson Score	-0.84	-1.56 - -0.12	p<0.001
NCCN	-0.48	-1.80 - 0.84	p<0.001
Baseline Score	-44.33	-47.04 - -41.62	p<0.001
Interval	0.80	0.01-1.59	p<0.001
Moderate/Big Bother Sexual Score			
EBRT	0.97	-0.88 - 2.81	p<0.001
Age	-0.04	-0.14 - 0.07	p<0.001
Charlson Score	-0.34	-0.86 - 0.19	p<0.001
NCCN	0.44	-0.48 - 1.36	p<0.001
Baseline Score	-30.51	-31.99 - -29.04	p<0.001
Interval	-4.58	-5.18 - -3.97	p<0.001
≥ 1 PPD			
EBRT	16.56	14.35 - 18.76	p<0.001
Age	-0.19	-0.32 - -0.06	p<0.001
Charlson Score	-0.71	-1.33 - -0.09	p<0.001
NCCN	-0.19	-1.34 - 0.96,	p<0.001
Baseline Score	-49.99	-53.45 - -46.52	p<0.001
Interval	-11.55	-12.28 - -10.82	p<0.001

Bolded values were considered statistically significant at p<0.001

Chapter 9: Discussion

Key Findings

This thesis significantly contributes to understanding late treatment-related genitourinary toxicity in prostate cancer patients treated with ERBT. The first few chapters within the thesis highlight that treatment-related toxicity is more common than previously thought. Furthermore, these chapters also describe the burden of treatment of these complications in the real-world clinical setting and at a state population level. The thesis demonstrates that toxicity can be predicted and provides a reliable tool for clinicians to use when counselling patients with localised prostate cancer regarding treatment options. The thesis then compares the toxicity of each treatment option in terms of hospital admissions and patient-reported outcomes. Each chapter contributes pertinent findings, as detailed below.

Firstly, the systematic review confirms that very few high-quality studies include five-year toxicity outcomes (n=6). None included 10-year toxicity outcomes. Meta-analysis revealed high five-year pooled estimates of genitourinary toxicity (17% [95% CI: 5-20%] RTOG vs 33% [95% CI: 27-38%] CTCAE) and highlighted the difficulty in accurately recording toxicity data due to different grading systems. Moreover, there were high five-year cumulative incidence estimates of haematuria (5% [95% CI: -4-14%]), urinary incontinence (12% [95% CI: 6-18%]) and urinary retention (24% [95% CI: 9-40%]).

Secondly, the prospective single-institution study described the high burden of elective and emergency urology workload attributed to late pelvic radiation toxicity, accounting for 3% of the 1,524 urology admissions over 12 months. Furthermore, this study determined that patients with prostate cancer treated with EBRT commonly present with late genitourinary toxicity occurring ≥ five years after radiotherapy (median [range] 7 [0-23] years), which is outside the usual duration of RCTs. In addition, patients with prostate cancer who developed genitourinary toxicity five years after radiotherapy had a higher median [range] RTOG grade (4 [3-4] vs 3 [2-4], p = 0.037) compared to those who developed toxicity earlier. They also had a higher proportion of emergency admissions (37/69 = 54% vs 10/31 = 32%, p = 0.048) and clot retention (28/69 (41%) vs 2/31 (6.5%), p < 0.001). Three (3/46, 7%) patients were diagnosed with radiation-associated secondary malignancy. Of these three patients, two had prostate cancer treated by brachytherapy over ten years previously (2/39, 5%) and were found to have LGpTa and HGpT2 urothelial carcinoma (UC) of the bladder. The remaining patient had vulval cancer, which was treated with EBRT and was subsequently diagnosed with LGpTa UC bladder. The median (IQR) time from radiotherapy to radiation-associated secondary malignancy was 10 (7.5, 10.5) years.

Thirdly, the population-level cumulative study determined that genitourinary complications after EBRT for prostate cancer are common. The ten-year cumulative incidence of hospital admission (28.4% [95% CI 26.3 – 30.6]) and procedures (18% [95% CI 16.1-19.9]) exceeds typical estimates. Of the 2,545 hospital admissions, 1,040 (41%) were emergency admissions, and 1,893 (74%) were readmissions. The median length of stay was five days. This study also determined several independent clinical predictors of genitourinary toxicity requiring admission, including diabetes (HR 1.28 [95% CI 1.08-1.53], p=0.004), smoking (HR 1.67 [95% CI 1.40- 2.00], p<0.001) and bladder outlet obstruction, especially without TURP (HR 5.87 [95% CI 4.8-7.17], p < 0.001). The multivariable analysis also determined a protective effect associated with TURP before radiotherapy and genitourinary toxicity

amongst patients with bladder outlet obstruction (HR 3.6 [95% CI 3.01-4.46], p < 0.001). The date of radiotherapy was not an independent predictor of genitourinary toxicity after adjustment for age, comorbidity, smoking and bladder outlet obstruction in multivariable analysis (HR 0.87 [95% CI 0.72-1.04], p=0.12).

Next, the predictive model study demonstrates the feasibility of predicting radiotherapy-related genitourinary toxicity requiring hospitalisation utilising pre-treatment clinical characteristics for men with localised prostate cancer. Clinicians in the preoperative counselling setting could use our nomogram to inform patient selection based on treatment-related toxicity. The decision curve analysis revealed that using this model led to a significant net benefit to patients from a threshold probability of five percent (i.e. extremely great concern regarding disease). Therefore, radiotherapy should be avoided in at-risk patients unless the patient or clinician has a significant concern about the disease process and little concern about treatment-related toxicity. An alternative interpretation of this analysis is to rephrase the results in terms of harm avoidance. For example, when radiotherapy is avoided amongst these at-risk patients, there are predicted net reductions in hospitalisations due to genitourinary toxicity in 38/100 and 63/100 patients at risk threshold probabilities of 20% and 50%, respectively.

Next, the comparative study determined that EBRT was associated with a higher 10-year cumulative incidence of genitourinary admission (40% [95% CI 35-44] EBRT vs 18% [14-21] RP, p<0.001) and GI admission (24% [95% CI 20-27] EBRT vs 3% [1-5] RP, p<0.001). The 10-year cumulative incidence of incontinence-related admission was lower after EBRT than RP (4% [95% CI 1.5-6.4] vs 8 [95% CI 6-10], p < 0.001). Amongst patients treated by contemporary techniques (n=2,673 (n= 1,462 RP ≥2010 vs

n=1,211 EBRT ≥2010; Appendix 2), EBRT was still associated with a higher 10-year cumulative incidence of genitourinary (40% [95% 25-52%] vs 17% [11-23%], p=0.001) and GI (18% [13-23%] vs 3.4% [1.1-5.6%], p < 0.001) hospital admissions compared to RP. EBRT was associated with a significantly greater risk of recurrent hospital admissions overall (HR 1.80, 95% CI 1.60-2.10, p = 0.0001) and admissions related to GI toxicity (HR 4.62 (95% CI 1.32-16.2, p=0.02), in a Prentice-Williams-Peterson counting process model adjusted for Charlson score and treatment year. However, there was no statistically significant difference in recurrent admissions related to genitourinary toxicity between treatment groups (HR 1.25, 95% CI 0.67-2.35, p=0.5). Compared to EBRT before 2010 (n=1,088 [47%]), patients treated with EBRT from 2010 onwards (n=1,250 [53%]) had a higher 10-year cumulative incidence of any hospital admission (100% [95% CI 100-100] vs 97% [95% CI 96-95%], p < 0.001) and genitourinary-related admission (36% [95% CI 31-40] vs 19% [18-21], p < 0.001). Furthermore, there was no significant difference in the 10-year cumulative incidence of GI-related admission (9% [95% CI 8-10] vs 10% [9-10], p = 0.2). This data suggests that although there continue to be advancements in radiotherapy techniques, patients and physicians should be aware of the risk of late toxicity when choosing between treatment options for prostate cancer.

Finally, the PROMS study determined significant differences in patient-reported outcomes for localised prostate cancer, even when considering contemporary techniques and adjusting for differences in baseline patient characteristics and function. Bowel domain scores were worse after EBRT compared to RP (beta -0.46, 95% CI -1.20 - -0.28, p<0.001), with a greater percentage of patients experiencing declines that exceeded the MCID at 12 months compared to baseline (22 vs 11%, p=0.009). Moderate/big bowel bother scores were significantly higher in the EBRT cohort at baseline and all follow-up periods compared to RP (beta -8.27, 95% CI -10.21- -6.34, p<0.001). Pad use (i.e. ≥ 1) per day was significantly lower amongst the EBRT group (beta 16.56, 95% CI 14.35 - 18.76, p<0.001).

Despite adjusting for contemporary techniques, EBRT was associated with worse bowel domain scores at 12 (75 vs 80, $p<0.05$) and 60 months (75 vs 80, $p<0.05$) than RP. Understanding the toxicity profile and patterns associated with these contemporary treatment options for localised prostate cancer could inform shared decision-making between patients and their clinicians in the pre-treatment counselling setting.

Significance

Overall this thesis has several significant contributions to the literature on treatment-related toxicity amongst men with prostate cancer. Firstly, it is the first to provide a comprehensive assessment of the incidence of toxicity requiring hospital admission following EBRT in patients with prostate cancer. Moreover, unique descriptions of the treatment burden associated with treatment-related complications amongst patients with prostate cancer are provided from the real-world single institution setting and from population-level registry data. Furthermore, the thesis is the first to develop a validated model to predict toxicity necessitating hospital admission. Unique models are also developed to determine recurrent hospital admissions related to treatment-related toxicity after EBRT and compared to RP amongst men with localised prostate cancer. Finally, the thesis includes a unique description and comparison of PROMS amongst men with prostate cancer treated by contemporary techniques. Each chapter within the thesis has its unique contributions to the literature.

The systematic review and meta-analysis study provides five primary novel contributions to the literature. Firstly, this study provides the first consolidated literature review and meta-analysis on long-term genitourinary outcomes in patients with prostate cancer treated with primary IMRT. Secondly, the meta-analysis demonstrates a pooled 5-year cumulative incidence grade >2 toxicity that exceeds typical reports (RTOG 17% [95% CI: 5-28%], CTAE 33% [95% CI: 27-38%]). The considerable difference in rate between the scoring systems highlights the difficulty in accurately capturing significant toxicity using scoring criteria. The 16% underestimation of genitourinary toxicity in the current study exceeds the 10% underestimation by RTOG compared to CTCAE. (235) The overall high risk for all included studies was primarily due to outcome assessment by unblinded treating clinicians, suggesting that the pooled cumulative incidence may be an underestimation.

Thirdly, subgroup meta-analysis revealed no significant difference in RTOG Grade ≥2 genitourinary toxicity at 60 months post-radiotherapy amongst men with localised prostate cancer treated with normofractionation compared with hypofractionation (HR 1.07, 95% CI: 0.91, 1.26, p = 0.41), based on a random effects model.(230, 233, 234) Fourthly, the heterogeneity in toxicity grading systems and bias in outcome assessment highlights the need for studies assessing other surrogate measures of toxicity, such as hospitalisation rates and patient-reported outcomes. Finally, the review also highlights the lack of high-quality studies reporting 60-month (n=6) and 120-month follow-up endpoints (n=0/6), time to event analysis (n=1/6; (232)), predictive factors (n=1/6; (230)) or economic evaluation (n=0/6).

Next, the prospective single-institution study provides a unique insight into the burden of radiation toxicity across various hospital environments, including inpatient, outpatient, emergency and elective settings. This prospective study demonstrates a high burden of elective and emergency urology workload attributed to delayed pelvic radiation toxicity in patients with prostate cancer. Furthermore, patients with prostate cancer who presented with late genitourinary sequelae ≥ five years after radiotherapy were associated with higher median RTOG grade toxicity (p = 0.037) as well as more frequent emergency admissions (p = 0.048) and radiation-induced haemorrhagic cystitis with urinary clot retention (p < 0.001). Delayed genitourinary toxicity following radiotherapy may result in particularly complex urological presentations and burden of care in the long term.

The state-population-based cumulative incidence study presents three main novel factors. Firstly, this is one of few studies to evaluate the 10-year cumulative incidence of treatment-related genitourinary complications requiring hospitalisation following radiotherapy for patients with clinically localised prostate cancer at a population level and the first in Australia. The high 10-year cumulative incidence

(28.4%) of hospital admission due to treatment-related genitourinary toxicity exceeds previous estimates following primary EBRT. (93, 187, 251) The date of radiotherapy made a minimal difference in the 10-year cumulative incidence of genitourinary toxicity-related admission amongst patients in this cohort. The date of radiotherapy treatment was not an independent predictor of genitourinary toxicity after adjustment for age, comorbidity, smoking and bladder outlet obstruction in multivariable analysis (HR 0.87 [95% CI 0.72, 1.04), p=0.12; Table 4).

Secondly, this is also the first Australian study to determine the volume of admissions and urological procedures for the management of radiotherapy treatment-related genitourinary complications at a population level. Greater than one-third of genitourinary toxicity-related hospital admissions occurred in the emergency setting. There were a significant number of admissions with a prolonged length of stay exceeding 48 hours. A significant number of patients (18%) required an invasive urological procedure. There were significantly fewer hospital admissions and procedures amongst patients treated with EBRT from 2010 onwards, which may reflect improvements in radiotherapy techniques or the shorter follow-up in this group, which likely underestimated late toxicity.

This is one of few population-level studies to determine pre-treatment clinical predictors of genitourinary-toxicity-related hospital admission. (187, 242, 251) We determined that patients with prostate cancer and concurrent bladder outlet obstruction without TURP prior to EBRT had the highest 10- year cumulative incidence of hospitalisation for treatment-related genitourinary toxicity (77% [95% CI 70%, 82%], p <0.001), in competing risk regression analysis. The strong relationship between patients with bladder outlet obstruction without TURP prior to EBRT remains statistically significant in multivariable analysis, adjusted for age, diabetes, smoking and year of treatment (HR 5.87 [4.80-7.17],

p < 0.001). Furthermore, patients with bladder outlet obstruction without TURP before EBRT had the highest frequency of emergency admissions (136/246 [55%] vs 273/3104 [8.8%], p < 0.001) and readmissions (110/246 [45%] vs 282/3104 [9.1], p < 0.001), for treatment-related genitourinary toxicity (Table 1, Figure 3).

Next, the predictive modelling study provides three unique primary contributions to the literature. Firstly, this study presents a novel data-driven model for treatment-related genitourinary toxicity requiring hospitalisation based on pre-treatment clinical characteristics amongst patients with localised prostate cancer treated by curative intent EBRT. The model performed strongly in calibration at one (AUC 0.765) and five years (AUC 0.75). The model was discriminant (concordance index = 0.67, censor-adjusted c-statistic = 0.80) and is consistent with the most robust models in the literature. (262)

Secondly, this was the first predictive study for genitourinary toxicity after radiotherapy to assess model utility via decision curve analysis. The decision curve analysis consistently demonstrated net benefit in using the model compared to the treat-all approach above 5% threshold probability. In other words, using this model to avoid radiotherapy treatment in patients at-risk of toxicity leads to significantly increased net benefit compared to a clinician who treats all patients regardless of the presence of these factors. An alternative method of illustrating this concern is through harm minimisation. When radiotherapy is avoided amongst these at-risk patients, there are predicted net reductions in hospitalisations in 38/100 and 63/100 patients at threshold probabilities of 20% and 50%, respectively.

Thirdly, this study provides a nomogram to facilitate the implementation of this model in the pre-treatment clinical setting. Numerous other authors have valued the reliable prediction of radiotherapy-related toxicity amongst patients with prostate cancer because it could guide the allocation of patients

into treatment groups based on their probability of severe toxicity and improve the therapeutic ratio.(198, 287, 288) Patients at high risk of radiotherapy-related toxicity could be counselled about treatment alternatives, modifications (e.g. advanced planning corrections or dose-reduction), or deferrals.

Next, the study that determined and compared first and recurrent hospital admissions between patients with clinically localised prostate cancer treated with either RP or EBRT has two primary novel contributions to the literature.

Firstly, this is the first study to model recurrent toxicity events in patients with localised prostate cancer. Overall, EBRT was determined to be associated with significantly higher median (IQR) recurrent admissions (20 [9-75] vs 14 [6-52], $p < 0.001$; Table 5) and higher proportions of emergency admissions (20 [9-75] vs 14 [6-52], $p < 0.001$; Table 5). EBRT was associated with a greater risk of recurrent overall (HR 1.80, 95% CI 1.60-2.10, $p = 0.0001$) and gastrointestinal (HR 4.62 (95% CI 1.32-16.2, p=0.02) hospital admissions, after adjustment for Charlson score and treatment year. There was no statistically significant difference in the adjusted risk of recurrent genitourinary hospital admissions after EBRT compared to RP (HR 1.25 [95% CI 0.67-2.35], p=0.5).

Secondly, this is the first population-level study of patients with clinically localised prostate cancer treated with contemporary techniques (RP or EBRT from 2010 onwards) to compare the 10-year cumulative incidence of specific treatment-related toxicity. Amongst patients treated by contemporary techniques (n=2,673 [n= 1,462 RP ≥2010 vs n=1,211 EBRT ≥2010]; Appendix 2), EBRT after 2010 was associated with a higher 10-year cumulative incidence of genitourinary (40% [95% 25-52%] vs 17% [11-23%], p=0.001) and gastrointestinal (18% [13-23%] vs 3.4% [1.1-5.6%], $p < 0.001$) hospital admissions

compared to RP after 2010. (Table 3) EBRT after 2010 was associated with a higher 10-year cumulative incidence of haematuria (30% [95% 13-44%] vs 5.6% [3.1-8.1%], p<0.001) and urinary fistula (0.6% [<0.1-1.2%] vs 0% [0-0%], p = 0.045) admissions. RP after 2010 was associated with a higher 10-year cumulative incidence of urinary incontinence (0.6% [95% CI 0.2-1.0] vs <0.1 [95% CI 0.2-1.0], p < 0.001).

Finally, the PROMS study has two main novel contributions to the literature. Firstly, this is the first study to directly compare EPIC-26 scores amongst a prospective population-level cohort of men with clinically localised prostate cancer treated with contemporary techniques over five years of follow-up. Despite the use of contemporary radiotherapy techniques amongst patients with localised prostate cancer, EBRT from 2010 onwards was associated with significantly worse 12 and 60-month bowel domain scores and higher percentages of MCID at 12 months (21% vs 10%, p = 0.008) than RP after 2010. Patients treated with EBRT from 2010 had lower pad use per day at 12, 24, and 60 months and better urinary incontinence scores at 60 months (87 vs 89, p < 0.05), but there was no statistically significant difference in MCID in either group (p > 0.05). However, whilst urinary incontinence scores improved over time in the RP ≥ 2010 group, they progressively deteriorated in the EBRT ≥ 2010 group. Similarly, the proportion of patients requiring daily pads, whilst higher post-RP≥ 2010 (p < 0.05), was increasing over time post-EBRT ≥ 2010.

Secondly, this study demonstrated that the impact of EBRT on moderate/big urinary bother greatly exceeds previous estimates. We found that the mean percentage of moderate/big urinary bother was higher amongst the EBRT group at baseline and 12 and 24-month follow-up intervals. The mean percentage of moderate/big urinary bother was lower at 60-month interval follow-up following EBRT (beta = -4.75, 95% CI -7.26 - -2.24, p<0.001); however, this may be due to the low sample sizes remaining at 60 months with evaluable data (n= 363, RP vs n = 38, EBRT). The impact of EBRT on late

patient-reported urinary toxicity far exceeds that reported by the recent ProtecT trial, which reported that urinary voiding and dysuria were similar between groups at 12 months. (302)

Strengths

The overall thesis on treatment-related toxicity amongst men with prostate cancer has several notable strengths, including a clear definition of the current problem, a thorough evaluation, rigorous methodology, and outcome reporting standards.

The introductory chapter clearly defines the problem associated with treatment-related toxicity after radiotherapy among patients with prostate cancer. The introductory chapter also highlights the gap in the literature regarding the incidence and prediction of late genitourinary toxicity. Furthermore, the systematic review of the literature and meta-analysis determines the scope of the problem associated with late genitourinary toxicity and its likely underestimation in the limited available data.

The incidence of radiation-associated genitourinary toxicity is initially described through systematic review and meta-analysis. The incidence is further evaluated using population data from the local cancer registry linked to all major hospitals within the state.

The systematic review included high-quality studies involving patients with prostate cancer treated using contemporary radiotherapy techniques and assessed using standardised toxicity grading systems. The meta-analysis appropriately used a random-effects model to account for the heterogeneity in the treatment characteristics among the included studies reporting RTOG toxicity (I^2 98%). The subgroup analysis of patients treated using either normofractionated or hypofractionated EBRT significantly reduced this heterogeneity (I^2 0%).

The state population-level incidence study benefits from a combination of population-level data and a long duration of follow-up. Most other key studies in the literature involve high-volume centres (188, 251, 252), randomised controlled trials (255, 256) or report follow-up periods of five to ten years. (182, 194, 289) The focus on patients treated with EBRT, and the exclusion of combination or other radiation modalities, reduces the heterogeneity within the treatment group and improves the accuracy of toxicity estimates. The use of hospital admission and procedure codes leads to highly interpretable toxicity estimates. Other studies are limited by significant heterogeneity in recording and reporting treatment-related toxicity, which can include a range of toxicity grading systems as well as specific physician-assessed (182, 291, 292) and patient-reported (181) outcomes. Furthermore, administrative data coding has been validated in other claims-based studies, which also assess severe pelvic adverse effects after radiotherapy. (277)

The events for the overall and specific treatment-related hospital admissions are subsequently compared between men with localised prostate cancer treated by either EBRT or RP. Clear comparisons of recurrent events for overall, gastrointestinal and genitourinary hospital admissions were presented using Mean cumulative function estimate plots. In literature, MCF is also called cumulative mean function (CMF) and is widely utilised in exploring recurrent event data. (298)

Subgroup analysis was performed on a cohort of patients treated using contemporary techniques (i.e. RP or EBRT from 2010 onwards) to reduce heterogeneity within the treatment groups, given the transition to contemporary techniques (e.g. robot associated laparoscopic prostatectomy and intensity-modulated radiotherapy) that occurred during this time.

The burden of treatment associated with these treatment-related adverse events is also described by the population data and is supplemented by prospective real-world data from a single tertiary centre.

The prospective single-institution study provides additional retrospective confirmation of the radiation-related aetiology of toxicity events through medical chart review.

The experiences of patients affected by these toxicities are also addressed through the evaluation of PROMS. Whilst the main focus is on genitourinary toxicity, the thesis also addresses other complications, including overall and radiation-induced gastrointestinal toxicity-related hospital admission. The thesis also compares adverse event outcomes relative to older EBRT techniques to assess for changes over time. Similarly, the thesis also includes a comparison of both admission and patient-reported outcomes between EBRT and RP, the primary alternative treatment for patients with localised prostate cancer. The thesis includes an internally validated model for predicting genitourinary toxicity and a detailed assessment of its performance.

Rigorous methodological techniques are used in each of the included chapters within the thesis.

The systematic review and meta-analysis study determines the risk of bias for each included study using validated instruments, including the Newcastle-Ottawa scale and the Cochrane Risk of Bias (RoB 2) Tool for non-randomised and randomised studies, respectively. The Cochrane Risk of Bias (RoB 2) Tool is the recommended instrument for the quality assessment of randomised controlled trials included within a systematic review. As described, the tool assesses six domains of potential bias, including selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases. Similarly, the study attempts to evaluate the effect of publication bias on the meta-analysis results; however, this was limited by the small number of studies included. The detailed appraisal of the quality of the included studies provided in the review increases its methodological rigour and the robustness of the reported results.

Next, the predictive study involved a multivariable model, which was determined through a backward elimination variable selection process with 2-sided alpha = 0.05. (282) The model is one of few to utilise

a backward variable feature selection process (181, 290), with others using less rigorous techniques such as forward feature selection (194, 291), Stepwise (289) or Lasso (198) methods. Collinearity among the variables was assessed using correlation coefficients. The large cohort also benefitted the identification of predictive factors, compared to other models in the literature, which tended to be developed within small cohorts with relatively fewer toxicity-related events (n <500 (181, 198, 274, 289) vs n = 500-1000 (264, 288)).

The model assessment was performed by the ABCD approach put forward by Steyerberg et al. (283). The proportional hazards hypotheses were tested by Schoenfeld's residual method. Model discrimination was determined using a censor-adjusted c-statistic. Model calibration was demonstrated with a calibration plot generated using bootstrap resampling (n= 10,000), and the Area under the Receiver Operating Characteristic Curve (AUC) was determined. The few other models of genitourinary toxicity after EBRT are limited by inconsistent performance reporting, with some studies only providing calibration plots. (194, 197, 288) Other studies appeared less discriminative, including the model presented by Yahya et al. with a large range in internally validated AUCs (AUC range 0.467 - 0.794) (262), or by De Langhe 2014, which reported AUCs dependent on multiple genetic markers (AUC 0.80 [markers included] and 0.67 [markers excluded]), (198) or by Ino Kuchi et al. which only included a singular significant variable (V75 of the bladder neck, AUC 0.72; $p < 0.0001$). (291)

Internal validation was performed using a penalised Cox model by adaptive elastic-net regularisation, which can outperform Lasso on data with highly correlated predictors. (284) Ten-fold repeated cross-validation was used, which is a more robust internal validation method than bootstrapping because it aims to counter the over-optimism associated with the latter method. (285) Similarly, repeat k-fold cross-validation (n= 10 folds, repeated 100 times) was used because it is a more robust process than bootstrapping. Like our study, most other model studies were also internally validated using resampling techniques (262, 288) (i.e. bootstrapping (288) vs split training set (182)). Some other studies did not comment on validation. (291)

The model utility was demonstrated using Decision Curve Analysis, which determined a significant net benefit to patients in using the model to avoid treatment-related genitourinary toxicity.(286)

The comparative admission study minimises potential confounders by including age, comorbidity and year of treatment in the multivariable recurrent event model. Similarly, the study excludes men with concurrent bladder cancer because their surveillance requires multiple cystoscopic procedures, which could be incorrectly attributed as a treatment for a prostatectomy-related complication. The Prentice William-Peterson Counting process model, which was used in the analysis, provides a stricter estimate of the risk of recurrent admission because it assumes that recurrent events within a subject are related and baseline hazard varies from event to event. (296, 297)

The PROMS study included random effects mixed linear regression, which was adjusted for age, comorbidity, NCCN disease risk and baseline EPIC-26 score. The PROMS study also compared the proportion of patients with a deterioration in PROMS that reached the minimal clinically important difference (MCID) at each interval between the treatment groups. The MCID presents the amount of change that results in a clinically discernible difference to patients. MCID was defined as 12 points for sexual function, (305, 310) 6 for urinary incontinence, (305, 310) 5 for urinary irritative symptoms, (305, 310) 4 for bowel function, (310) and 4 for hormonal function (305, 310) according o the literature. The bother items were dichotomised into moderate/big bother, and small/very small/no bother, consistent with cut-off points reported elsewhere. (218, 309, 311, 312)

All reported outcomes are reported according to recognised standards, including the PRISMA checklist for the systematic review and meta-analysis, the STROBE statement for the observational studies and the TRIPOD checklist for the predictive model.

The review has a rigorous and methodical approach because it utilises the PRISMA protocol in describing the rationale, hypothesis, and proposed methods of the study. In addition, the systematic review study protocol was prospectively registered with PROSPERO, an international prospective systematic review registry (CRD42019133320). By registering this protocol prior to the commencement of searches, it became possible to compare the proposed protocol with the subsequently reported review findings. The high correlation between the protocol and the reported data confirms the integrity of the researchers. All named contacts in the protocol are considered accountable for the accuracy of the content reported.

The observational studies of the incidence and burden of treatment of treatment-related toxicity included within the thesis were each conducted according to the STROBE statement. (322) The STROBE statement is a transdisciplinary initiative which aims to improve the reporting of observational research.

The model development process was conducted following the TRIPOD checklist. (281) The TRIPOD checklist aims to standardise the reporting of observational studies which develop, validate or update a prediction model for either diagnostic or prognostic purposes. (281)

Limitations

Overall the thesis has several limitations. First and foremost, there was limited data available in the observational studies regarding the specific type of EBRT technique used, including IMRT, VMAT and hypofractionation. Whilst the SA-PCCOC registry lacks data on EBRT delivery technique, several other studies have also reported an inconsistent reduction in treatment-related late genitourinary toxicity despite technological improvements in prostate EBRT delivery (i.e. intensity-modulated radiotherapy and image-guided radiotherapy. (114-116, 294) The year 2010 was used in the cancer registry study as a proxy for contemporary radiotherapy techniques, given that the transition to newer techniques occurred in South Australia at approximately this time, as per A/ Professor John Leung, the Radiation Oncologist included in the supervisor list. The predictive modelling study was particularly restricted by our inability to specify the type of EBRT used for the treatment of the included patients. We also lack information regarding radiation field size, and nodal treatment is expected to lead to more toxicity compared to the prostate alone. However, the clinical risk factors included in the predictive model in the current study remained significant in multivariable analysis adjusted for the year of treatment. Fortunately, models to predict toxicity based on radiation treatment-specific factors have already been described and are typically already incorporated into contemporary computerised radiotherapy planning and delivery systems.

Furthermore, the impact of newer radiotherapy delivery techniques on treatment-related toxicity was addressed in the systematic review through subgroup analysis of the three studies, including a comparison of hypofractionated and normofractionated radiotherapy. (230, 233, 234) Subgroup analysis was also performed in the single-institution study for men with missing radiotherapy technique data to confirm the proportion of patients with clinically proven radiation-induced toxicity and association with radiation treatment. However, three pivotal trials have been excluded from our SR as they did not meet the inclusion criteria and deserve dedicated discussion.

Firstly, the Fox Chase trial by Pollack et al. (2013) included (n = 307) men with localised prostate cancer treated with either CIMRT (n=152) or HIMRT (n=151) between 2002 – 2006.(6) The 5-year revised cumulative risks of RTOG grade ≥ 2 late genitourinary adverse effects for the CIMRT and HIMRT patients were 13.4% (95% CI, 8.0% to 20.1%) and 21.5% (95% CI, 14.4% to 29.6%) with no overall difference (P = .16).) (6) However, pelvic nodes were treated in those with high-risk disease (n = 51, 33.5% CIMRT Arm and n = 53, 35% in HIMRT Arm). (6) Therefore, this trial was excluded due to the wrong intervention being performed.

Secondly, we were unable to include the MDACC trial in the meta-analysis because it did not report 5-year outcomes; however, we have included the 8-year toxicity data in the discussion section. The MDACC trial by Hoffmann et al. had an 8.5-year median follow-up and reported an 8-year cumulative incidence of RTOG grade 2 or 3 genitourinary toxicity of 16.4% (95% CI, 10.4% to 25.4%) in the conventional arm and 15.1%(95% CI, 9.4% to 23.8%) in the hypofractionated arm (P=.84).(7)

Thirdly, the Hypo-Flame trial by Draulans et al. (2020), only reported 90-day toxicity rates and was unable to be included in our study. (8)

In addition, this review does not evaluate the long-term toxicity associated with nodal irradiation or radiotherapy following radical prostatectomy, which exposes larger portions of adjacent normal tissue to radiotherapy, and which is likely also underreported. However, this aspect was considered during the study protocol conception, where we decided to focus on men with non-metastatic prostate cancer with curative intent primary prostate IMRT without nodal irradiation for three main reasons. Firstly, the late toxicity amongst this group is poorly described and underestimated. Whilst toxicity following nodal irradiation is well known, the toxicity rates in men with localised prostate cancer treated with modern techniques, such as IMRT, are thought to be minimal. Secondly, to reduce heterogeneity amongst the population and treatment-related characteristics to increase the suitability for meta-analysis of the results. Unfortunately, the included studies did not contain comparator arms of patients

treated with nodal irradiation, so subgroup analysis was not possible. Finally, a substantial volume of studies (n = 4,699) was initially identified in the systematic review. We decided to narrow the scope of the study to published prospective studies of treatment-related toxicity after curative intent prostate EBRT without nodal irradiation to ensure that we were evaluating only high-quality homogenous studies. Most of the excluded studies were retrospective and often lacked a systematic application of validated instruments in determining late toxicity outcomes, which can further increase the potential for under-reporting toxicity events.

Similarly, the thesis does not address the toxicity associated with other techniques, such as brachytherapy, which may be used alone or in combination with EBRT. It is expected that radiation-induced toxicity would be increased following treatment in these settings and warrant a similar level of scrutiny. This thesis focuses on EBRT to reduce heterogeneity in the radiotherapy treatments given to enable accurate determination of the incidence of toxicity and comparisons between contemporary and outdated EBRT techniques as well as between EBRT and RP.

Similarly, most of the thesis focuses on genitourinary toxicity outcomes and lacks an assessment of gastrointestinal toxicity, which is more common. Genitourinary toxicity was selected as the primary outcome to be assessed in the thesis because it is less common and is relatively under-researched, especially in terms of long-term data, compared to gastrointestinal toxicity. However, gastrointestinal toxicity has been included in the single institution chapter and the later chapters comparing admissions and patient-reported outcomes between patients with prostate cancer treated by either EBRT or RP.

The thesis also does not provide a detailed analysis of radiation-associated secondary malignancy. Whilst the proportion of patients with secondary primary urothelial carcinoma of the bladder was reported in the single institution study, no further assessment of the incidence of radiation-associated secondary malignancy was performed. Had the data been available, the studies included in the systematic review, then meta-analysis could have been performed to determine the pooled cumulative incidence of the secondary primary malignancy. Unfortunately, secondary primary malignancy was not available from the SA-PCCOC registry or the ISAAC hospital administrative database.

Impact

This thesis and its associated peer-reviewed publications and conference presentations can be expected to have two direct impacts on current practice.

Firstly, the studies highlighting the incidence of radiotherapy-related toxicity and the associated treatment burden may lead to improved counselling of patients in the pre-treatment setting. In the author's clinical experience (anecdotal) as a Urology Registrar, patients with delayed radiotherapy-related toxicity requiring hospitalisation often complain that they were not counselled about these adverse events. Some patients report being informed that there are virtually no long-term side effects, particularly with contemporary EBRT techniques, such as VMAT and IMRT. Similarly, patients who have received neoadjuvant radiotherapy for cervical (323) or anal canal carcinoma (324) also present for toxicity and frequently complain that they did not receive sufficient counselling about these adverse events. Neoadjuvant radiotherapy for cervical and anal canal carcinoma has emerged as a standard of care, and the burden of treatment associated with radiotherapy toxicity is expected to increase. (247) Whilst non-prostatic pelvic malignancy was not a focus of this thesis, the burden of treatment is described in the prospective single-centre study.

In the author's clinical experience (anecdotal), patients with prostate cancer who undergo radical prostatectomy often voice decisional regret because of their post-operative urinary incontinence or erectile dysfunction. The novel systematic review by Christie et al. in 2015 evaluated nine studies that included a comparison of decisional regret amongst men with prostate cancer treated with either EBRT or RP. (156) Five studies demonstrated higher regret following RP than EBRT, (325-329) but only one study reported a statistically significant difference. (329) Two studies demonstrated higher decisional regret amongst men with prostate cancer treated with EBRT than RP. (156, 330) However the difference was not statistically significant in one study (330), and not reported in the other. (156) The remaining two studies reported no statistically significant difference in decisional regret amongst

men with prostate cancer treated with either EBRT or RP but lacked reporting of specific outcome details. (331, 332) However, only one included study had a median follow-up over five years (5.5 years median). (333) This study by Nguyen et al. (333) included a much lower proportion of men with prostate cancer treated with EBRT than RP (n = 237 vs n = 410) and reported a 14.8% overall rate of decisional regret (HR 0.8, p = 0.377).

The validated predictive model and nomogram provided in the thesis offer a practical tool for clinicians to use in pre-treatment patient counselling. The utilisation of this tool, as demonstrated in decision curve analysis, may lead to a significant reduction in patients who develop treatment-related toxicity. As a clinician who has liaised with radiation oncologists across two urology centres within South Australia, the author has noticed an increased interest by Radiation Oncologists towards patient risk factors for toxicity during multidisciplinary oncology meeting discussions. For example, when a patient with clinically localised prostate cancer is discussed for a consensus on local curative treatment, there is increased interest regarding the patient's baseline urinary function and whether a TURP is planned.

Secondly, the thesis highlights the need for better follow-up of patients with prostate cancer treated with radiotherapy to monitor for delayed toxicity. Most patients with delayed toxicity identified in the prospective and population studies had completed their radiation oncology follow-up, and their subsequent development of treatment-related toxicity requiring hospital admission under the urology service would have remained unknown to their treating clinician. No patient with radiation-related toxicity in the prospective single-centre study was consulted by the radiation oncology team either as an inpatient or outpatient. The high incidence and burden of treatment associated with radiation-related toxicity in patients with prostate cancer presented in this thesis highlight the need for a single reliable system to record radiation treatments and long-term outcomes. For example, the international Prostate Cancer Outcomes Registry in Australia and New Zealand (PCOR-ANZ) could be an ideal

platform to improve the capturing of treatment-related toxicity. (334) In the shorter term, consideration should be given to increased consultation with radiation oncologists regarding patients who present with radiation-related toxicity to other inpatient teams. Alternatively, a hospital pathway whereby patients with radiation-related toxicity are admitted under radiation oncology to increase awareness of the frequency and often complicated nature of radiation-induced toxicity. For example, as seen in the prospective study, many patients with prostate cancer treated by EBRT who develop radiation-induced haemorrhagic cystitis are on antiplatelet (14/30, 47%) or anticoagulation (10/30, 33%) therapy. Difficult clinical decisions must be made regarding the cessation of these medications given the often-recalcitrant nature of radiation-induced haemorrhagic cystitis, which may require prolonged and recurrent emergency presentations with haematuria requiring catheterisation and operative haemostasis. These patients are often comorbid with a history of ischaemic heart disease (9 / 24 [38%]) and atrial fibrillation (6 / 24 [25%]).

Future work

Overall, there are four main directions for further extensions on the foundations established by this thesis. Firstly, a similar inquiry into the cumulative incidence of late treatment-related toxicity and predictive factors is required for other forms of radiotherapy, including brachytherapy, stereotactic ablative radiotherapy and proton beam radiotherapy. Brachytherapy is a big topic and would require categorisation into high dose and low dose rate and whether administered as brachytherapy alone or in combination with EBRT. The toxicity associated with stereotactic radiotherapy, including the recent development of Cyberknife, also warrants further scrutiny. (335) Despite increased advertising for Cyberknife, there remains limited evidence comparing outcomes post-Cyberknife to other cancer treatments. (336-341) Proton beam therapy also requires further investigation, given lacking data determining and comparing 10-year toxicity outcomes to other treatment options. (342, 343)

Secondly, future dedicated research into cost analysis should be considered, including an evaluation of cost burden and cost utility. Prostate cancer is the single most expensive disease in the Australian health system's expenditure, according to the Australian Institute of Health and Welfare.(344) Estimates based on the Pharmaceutical Benefits Scheme determine that prostate cancer alone accounts for 20% of overall cancer-related costs in Australia. (344) Similarly, Blakely et al. in a review of New Zealand's national cancer registry, estimates prostate cancer to be the third highest contributor of national public health expenses (6% of the total sum). (345) These studies highlight the increasing burden of prostate cancer on patients and health care systems. However, very few studies include a direct comparison of the costs associated with EBRT and RP for patients with localised prostate cancer. (346) There is also a paucity of cost data regarding the additional economic impact of adjuvant or salvage therapy on patients and institutions. The cost burden associated with the management of the treatment-related toxicities that patients may encounter because of their primary and subsequent

cancer treatments remains poorly described. There exists one population-based study by Kiechle et al. in 2016 involving 1,111 patients, which has retrospectively assessed the burden of the cost associated with radiation cystitis in Ohio. (347) Kiechle et al. determined that the median admissions cost was $7,151 USD. Most of the admission costs derived from endourological procedures (34.4%), followed by blood product transfusions (28.9%). Unfortunately, this study lacked cost data on other expensive treatment options, including hyperbaric oxygen therapy, which requires 40 inpatient sessions. This study also did not report cost efficacy or cost-utility due to its reliance on Medicare data. A more recent prospective single-institution study by Ma et al. calculated the cost of five patients with radiotherapy-related toxicity over nine hospital admissions in the private sector. The total cost for these nine admissions was $20,803.65 AUD, an average of $2,311.52 AUD per admission or $520.10 AUD per bed day. (188) Unfortunately, the study was unable to calculate the cost of patients belonging to the public sector, which may have been greater.

We intended to critically appraise articles containing economic analysis that met the inclusion criteria for our systematic review study. Per the systematic review protocol, articles containing economic analysis were to be assessed according to the Drummond Checklist (348), as used by Becerra et al. (224) in their systematic review of economic evaluation of treatment for localised prostate cancer in Europe. The quality was to be assessed according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement. The primary outcome to be extracted was the incremental cost per Quality-Adjusted Life-Year (QALY) gained. The secondary outcomes to be extracted were Incremental Cost-Effectiveness Ratios (ICERs) and comparative cost per treatment. However, none of the six included studies reported economic analysis. An updated systematic review of the cost associated with localised prostate cancer internationally should be considered and could be guided by our intended analysis as published in PROSPERO (CRD42019133320). This initial appraisal of the literature could form the basis of an additional thesis. Subsequent chapters of the thesis could include

an analysis of the cost burden regarding direct and indirect costs. Direct costs are ascertainable from institutions, whilst indirect costs may require prospective surveys to be fully captured, given recall bias, loss to follow-up and death. There would be potential to divide this inquiry into early and late costs, given the insidious natural history of post-irradiation genitourinary complications. Chapters on cost efficacy or cost-utility could also be considered, as guided by the results of a systematic review. A cost-comparative model using either cost-efficacy or cost-utility analysis could then be developed. Patients identified from the cancer registry could be prospectively assessed for cost analysis. The percentages of patients that change or have combination treatment modalities will need to be determined. The exploration of choice models, such as Discrete choice experiments, would be a natural extension of this proposed cost analysis thesis. (349, 350)

Thirdly, this thesis builds a convincing case for an RTOG RCT to include a detailed analysis of long-term genitourinary toxicity. The proposed RTOG RCT should include men with clinically localised prostate cancer treated with curative intent EBRT without nodal irradiation or radical prostatectomy. Toxicity outcomes should be assessed using hospital admissions and PROMS and recorded by clinicians not involved in the treatment of the included patients. Patient follow-up should be longer than previous RTOG trials and extend to at least ten years from the treatment date. A multi-institutional design should be considered, with the inclusion of a range of high and low volumes centres. Alternatively, a cluster RCT could be considered to estimate population-level outcomes. Subgroup analysis could be considered for men with concurrent clinically localised prostate cancer and bladder outlet obstruction due to BPH with and without TURP prior to radiotherapy.

Fourthly, the data presented in the thesis may motivate further investigations focusing on causal pathways, mechanisms of action and preventive strategies. Similarly, the thesis highlights the need for

further research into novel management options for patients with pelvic malignancy who undergo radiotherapy and develop treatment-related toxicity. Radiation-induced haemorrhagic cystitis continues to be challenging for the urologist to manage. (351) There remains no single reliable treatment for radiation-induced haemorrhagic cystitis, and most cases require prolonged bladder irrigation. (352, 353) Whilst several novel treatments have been investigated, including immunosuppression, intravesical botulinum toxin injection and vascular endothelial growth factor, further research is still required. (354) Each chapter included in this thesis has several avenues that would benefit from further inquiry.

Firstly, there is a need for further systematic review and meta-analysis of genitourinary toxicity following primary EBRT with pelvic irradiation, which involves a greater field of treatment and confers greater toxicity risk. Similarly, future work should address late genitourinary toxicity associated with adjuvant/ salvage EBRT, which involves larger portions of the bladder being exposed to radiotherapy. The outcomes of this additional review could be extended to include other pelvic toxicity, including gastrointestinal and secondary primary malignancy.

Next, future prospective single institutional studies should also determine the impact on patient's quality of life and the associated cost burden with genitourinary toxicity following pelvic radiotherapy. The significant burden of treatment demonstrated in the single-centre study highlights the need for further prospective multi-institutional studies. Ideally, patients with radiation-induced toxicity, including cystoscopically confirmed late radiation cystitis, urinary tract strictures and necrotic bladder neck contractures, could be flagged in a centralised regional registry. This registry could include patients with any pelvic malignancy treated with pelvic radiotherapy to more accurately capture the total burden of treatment at a regional level.

Next, there is a need for at least two further studies identified from the cumulative incidence of genitourinary toxicity study. Firstly, further prospective study is required to explore the relationship between bladder outlet obstruction and TURP prior to EBRT. The patient cohort could be identified using a similar data linkage process using a combination of cancer registry and hospital admission database information. There should be stratification to account for the sequencing of TURP and cancer diagnosis. For example, prostate cancer may be diagnosed incidentally during TURP; alternatively, a TURP may be performed after the prostate biopsy diagnosing prostate cancer when a subsequent bladder outlet obstruction workup is performed. The outcomes of this study should include a direct comparison of patient-reported outcomes. Secondly, further multivariable analysis of clinical predictors should incorporate specific **radiation treatments, including changes in field (IMRT/VMAT), dosing (hypofractionation) and delivery (Stereotactic Ablative Radiotherapy, Proton Beam Therapy).**

Next, we anticipate future opportunities to validate our predictive model against other cohorts externally. An ideal cohort for external validation would include patients with clinically localised prostate cancer treated with contemporary techniques only (180, 182), especially when long-term outcome data of such treatments are available. Future studies predicting toxicity outcomes following new forms of radiotherapy should include patient-specific clinical factors in their predictive models. Whilst our model focuses on genitourinary toxicity requiring admission, further predictive studies should also include other measures, such as patient-reported outcomes, in their modelling. Furthermore, other toxicity outcomes, such as gastrointestinal and secondary primary malignancy, should similarly be considered in future predictive modelling studies.

Next, a natural extension of the comparative treatment-related toxicity study would be the inclusion of the incidence of secondary malignancy in men with localised prostate cancer after cancer treatment. The potential risk of developing secondary malignancy after radiotherapy is a paramount concern for patients with clinically localised prostate cancer who are faced with the often challenging task of deciding between treatment options. Accurate knowledge of the incidence of treatment-related secondary primary malignancy following either radiotherapy or surgery would enhance patient-centred decision-making. Furthermore, while rates of secondary malignancies in post-RT PC patients have been assessed in epidemiologic studies, the pathologic features and distribution of these tumours compared to those in non-radiated patients are not well-documented. (170)

Several studies have identified an increased risk of developing secondary malignancy amongst patients with prostate cancer treated with radiotherapy, including urothelial cell and rectal carcinomas. (355-359) However, the definitive incidence of secondary primary malignancy remains unclear due to the diverse methodologies used in previous studies. The largest published population-level 5-year cumulative incidence study of treatment-related complications amongst patients with prostate cancer who underwent either radiotherapy (RT) (N= 16,595) or RP (N= 15,870) reported 5-9 year cumulative incidence rates of secondary primary malignancy of 4.5% (95% CI 3.8-5.5) and 1.8 (1.3-2.4), after RT and RP, respectively. (187) Whilst the most common secondary malignancy was from the GIT (87 per 100,000 person-years post-RT and 28 per 100 000 person-years post-RT, $p<0{\cdot}0001$), there was also an increased risk of genitourinary, lung and haematological secondary malignancy after RT ($p<0{\cdot}0001$). (187) Whilst this was a population-level study assessing hospitalisation, it did not specify the type of RT (75.6% had 3D-CRT, but included brachytherapy and stereotactic beam radiotherapy). It was also limited by its short duration of follow-up, which would have failed to capture late toxicity.

The importance of longer follow-up duration in diagnosing secondary malignancy was highlighted by Huang et al., involving (n = 2120) patients treated with different forms of EBRT or BT compared to a matched (1:1, age and follow-up time) surgical cohort extracted from a population-based cancer registry (Metropolitan Detroit Cancer Surveillance System, SEER, NCI). (360) Huang et al. determined that the use of EBRT for patients with prostate cancer in the matched-pair cohort was associated with a significantly increased risk of secondary malignancy at both five (HR 1.86, 95% CI 1.36–2.55) and ten (HR 4.94, 95% CI 2.18–11.2) years following treatment. (360) The most common sites of secondary malignancy diagnosis were the bladder, lymphatic system (i.e. lymphoproliferative malignancy) and soft tissue (i.e. sarcoma). (360) However, the study by Huang et al. had several limitations. Firstly, it did not include propensity matching of smoking status, which will likely act as a major confounder in the study. Secondly, the study included significantly outdated techniques, including two-dimensional EBRT. The study also reported that using more conformal radiotherapy techniques, such as three-dimensional EBRT, may be associated with a lower incidence of secondary primary malignancy. Thirdly, the mean follow-up period for the patients who underwent more contemporary and conformal treatment was almost half the duration of the patients who received two-dimensional EBRT (five vs nine years follow-up, respectively). Fourthly, the study also defined secondary primary cancer as a new primary malignancy that occurred from the commencement of treatment with either surgery or EBRT. This definition would have led to the overestimation of secondary primary malignancy, as it would have led to the inclusion of patients with synchronous malignancies.

In comparison, single institutional reviews have more accurate data but suffer from a limited number of patients. For example, the cohort study by Zelefsky et al. compared patients with localised prostate cancer treated with RP (n = 1348), EBBT (n=897) or BT (n=413) between 1998 and 2001. (169) In this study, Zelefsky et al. determined lower 10-year secondary malignancy-free survival rates following EBRT than RP (83% vs 89%, p = 0.002). However, the study did not determine a significant association

between treatment intervention and secondary malignancy in multivariable analysis when adjusted for older age (p=0.01) and smoking history (p<0.001). Among 243 patients who developed a secondary primary malignancy, the 5-year likelihood of secondary malignancy were 43.7% and 15.6% in the EBRT and BT groups, respectively, compared with 26.3% in the RP cohort (p=0.052). This study has several limitations, including its retrospective design and setting in a high-volume single institution centre. There was limited follow-up beyond twelve years after treatment, and most patients had an early diagnosis of secondary malignancy, which may have contributed to favourable survival outcomes amongst patients who developed secondary malignancy after EBRT. The study is also 20 years old, and patients' life expectancy and prostate cancer survivorship have increased since then, leading to a greater at-risk contemporary population. There were relatively small numbers of included patients in the study, likely due to the rarity of secondary malignancy. The importance of a longer median duration of follow-up was demonstrated by Brenner et al. [6], who reported increased relative risks of secondary malignancy at 5 and 10 years after external-beam radiotherapy (EBRT) of 15% and 34%, respectively. Similarly, Bhojani et al. (2010), from the Montreal Health Center (361) noted a higher incidence of rectal and lung cancers in EBRT-treated patients than in surgery-treated patients at 10 years after treatment (2% vs 1%, hazard ratio [HR] 2.0; and 7% vs 4%, HR 2.1, respectively). Their results, however, were derived from patients treated with EBRT before the availability of conformal-based techniques, with larger volumes of normal tissue being exposed to the radiation doses.

Therefore, there is a need for a study of men with clinically localised prostate cancer who have undergone treatment with either curative intent external beam radiotherapy or radical prostatectomy (open or robotic-assisted laparoscopic) with the primary aim of determining the 5–15-year cumulative incidence of secondary primary malignancy. Secondary aims should include a description and

comparison of patient demographics characteristics, including age, comorbidities, smoking history, and oncological characteristics (e.g. ISUP grade, TNM stage, NCCN risk category, baseline PSA). Subgroup analysis could be considered for patients with node-positive disease compared to localised prostate cancer. Similarly, subgroup analysis of patients treated with contemporary or older techniques should be performed.

The following hypothesis could be generated to be answered by this proposed study:

H0: For men with prostate cancer, treated with either curative intent radiotherapy or radical prostatectomy, there is no difference in the 5-15 year incidence of secondary primary malignancy.

Ha: For men with prostate cancer, treated with either curative intent radiotherapy or radical prostatectomy, there is a difference in the 5–15-year incidence secondary primary malignancy.

A range of secondary primary malignancy sites, which are supported by the literature, should be considered, including genitourinary (urothelial, renal), gastrointestinal, soft tissue, dermatological, haematological, lung, breast, otolaryngology, eye and CNS sites. (136) Men with localised prostate cancer may be candidates for either surgery/ EBRT, with multivariable adjustment for age and smoking history.

Further research is required to determine the ideal reporting standard for radiation-related toxicity. For example, the systematic review reported a higher 10-year cumulative incidence of grade >2 GU toxicity when reported with CTCAE (33% [95% CI: 27-38%]) compared to RTOG (17% [95% CI: 5-20%]) toxicity scoring systems. The subsequent chapters of the thesis assess hospital admission as a surrogate for grade 3 toxicity for these scoring systems. Whilst the use of hospital admission is a relatively blunt tool to assess severity, the high volume of hospital admissions data improves its accuracy. Whilst the use of a validated PROMS instrument is more reliable and rigorous, there is a paucity of data, especially beyond ten years from radiation treatment. No studies have compared hospital admission and PROMS data for patients with prostate cancer treated by radiotherapy who develop treatment-related toxicity. Unfortunately, we were unable to assess the correlation between our hospital admission data and PROMS due to insufficient data. However, further scrutiny of the correlation between PROMS and hospital admission data should be considered with a larger dataset. For example, the correlation between late EPIC-26 haematuria bother and hospital admissions for haematuria could be made. Furthermore, predictive modelling could be considered using PROMS, similar to the convincing predictive model based on hospital admission for genitourinary toxicity post-EBRT in the current thesis. The accuracy and performance of these models could then be compared.

A natural extension of the predictive and comparative analysis in this thesis would be the creation of a novel computerised clinical decision support system for patients choosing between radical prostatectomy and EBRT in terms of treatment-related toxicity. This tool could be developed using machine learning techniques, of which there are several options. Firstly, decision tree analysis could be considered, given its intuitive interpretation and lack of requirement for dummy variables. However, decision tree analysis is relatively less robust than other machine learning techniques. (362) Alternatively, random forest analysis could be considered, which can handle large datasets with high dimensionality. However, random forest analysis has a tendency to overfit noisy datasets. (363)

Another option is neural network analysis, which can be used for both regression and classification problems and performs well despite large numbers of inputs and layers. However, neural network analysis requires additional development time and computational power and is restricted by the need for numerical inputs. (364) Logistic regression with multivariable Cox proportional regression analysis has mainly been used in this thesis and is the most common tool for investigating the influence of several factors on the survival time of patients simultaneously. Whilst Cox regression performs reasonably well compared to machine learning models, it does not provide estimates of the degree of separation of the different subgroups.(365)

Conclusion

The current thesis demonstrates that treatment-related toxicity is common amongst men with localised prostate cancer treated by external beam radiotherapy. Furthermore, this thesis highlights that toxicity often occurs over five years after treatment, which exceeds the follow-up period included in most RCTs assessing adverse events. The included chapters within the thesis each contribute their unique concluding remarks.

Firstly, the rate of late genitourinary toxicity in terms of Radiotherapy Oncology Group (RTOG) and Common Terminology Criteria for Adverse Events (CTCAE) scores in prostate cancer patients treated with IMRT was determined through systematic review and meta-analysis. The systematic search revealed that there is a paucity of high-quality studies reporting 60-month toxicity rates after IMRT. The pooled estimated cumulative incidence of late toxicity based on meta-analysis, whilst high, ultimately remains conservative.

Secondly, the burden of treatment associated with treatment-related toxicity at a single institution was described. This prospective study highlighted that many patients with late genitourinary toxicity after pelvic radiotherapy present to a single tertiary-level hospital over five years after their initial treatment. A high burden of elective and emergency urology workload is attributed to patients with delayed pelvic radiation toxicity. The number of patients with radiation-associated secondary malignancy in this study (secondary bladder malignancy was detected in 7% of patients) following pelvic radiotherapy requires further research and assessment. Subgroup analysis of patients with prostate cancer treated with EBRT revealed that delayed genitourinary toxicity following radiotherapy is often particularly complex and leads to a high burden of care.

Thirdly, the cumulative incidence of treatment-related genitourinary toxicity amongst patients with localised prostate cancer treated with primary external beam radiotherapy was determined at a state population level. The cumulative incidence of treatment-related genitourinary toxicity after prostate EBRT exceeded typical reports. Despite advancements in EBRT delivery techniques, patients and their treating clinicians should be aware of the risk of late treatment-related genitourinary toxicity. Patient pre-treatment clinical factors significantly and independently influence the risk of treatment-related genitourinary toxicity. TURP before EBRT appears to partially reduce the risk of genitourinary toxicity for men with concurrent prostate cancer and bladder outlet obstruction.

Fourthly, a model was developed, assessed and presented for predicting genitourinary toxicity amongst men with clinically localised prostate cancer. The model was accurate, performed well, and demonstrated significant net benefit to patients in decision curve analysis. Clinicians in the preoperative counselling setting should use our nomogram to inform patient selection for local curative intent treatment for prostate cancer, which may avoid or at least minimise treatment-related toxicity.

Fifthly, the incidence of treatment-related toxicity was compared between patients with clinically localised prostate cancer treated with either EBRT or RP. In patients with clinically localised prostate cancer treated by either EBRT or RP, EBRT is associated with a significantly higher 10-year cumulative incidence of genitourinary and gastrointestinal toxicity-related admissions. In addition, EBRT use is associated with a significantly greater risk of recurrent hospital admissions overall and hospital admissions related to gastrointestinal toxicity despite adjustment for patient age, comorbidity and improvements in radiotherapy delivery technique.

Finally, the impact of treatment-related toxicity following EBRT or RP was determined and compared using PROMS. There were significant differences in PROMS after local curative treatment for prostate cancer despite adjustments for contemporary techniques. These differences in PROMS persist over five years after treatment. Understanding the associated toxicity patterns could inform shared decision-making during pre-treatment counselling.

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Appendices

Chapter 3: Appendix 1. PRISMA-P Checklist

		Reporting Item	Line Numbers
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1-3
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	5-16
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	5
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	287-292
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list	n/a

		changes; otherwise, state plan for documenting important protocol amendments	
Support			
Sources	#5a	Indicate sources of financial or other support for the review	298-300
Sponsor	#5b	Provide name for the review funder and / or sponsor	NA
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	NA
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	57-81
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	82-101
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	126-173
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial	106

		registers or other grey literature sources) with planned dates of coverage	
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	105-117
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	194-195
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	165-173
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	178-180
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	180-187
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	187-193
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at	197-207

		the outcome or study level, or both; state how this information will be used in data synthesis	
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	215-217
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	209-220
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	224-232
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	n/a
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	220-222
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	197-207

The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution License CC-BY 4.0. This checklist was completed on 27. June 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

Chapter 5: Appendix 1. STROBE checklist

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Line No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	28-32
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	32-39
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	48-61
Objectives	3	State specific objectives, including any prespecified hypotheses	63-67
Methods			
Study design	4	Present key elements of study design early in the paper	97-103

Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	72-78
Participants	6	(a) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	79-89
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	95-121
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	95-121
Bias	9	Describe any efforts to address potential sources of bias	136-140
Study size	10	Explain how the study size was arrived at	NA

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	132-136
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	127-131
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	139-140
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	102-103
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 1
		(b) Give reasons for non-participation at each stage	Figure 1

		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Table 1
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Table 2
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Lines 157-162 Table 3, Table 4

	(*b*) Report category boundaries when continuous variables were categorized	Table 1, Table 2
	(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	176-182
Discussion			
Key results	18	Summarise key results with reference to study objectives	190-210
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	292-308
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	212-290
Generalisability	21	Discuss the generalisability (external validity) of the study results	292-304
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	322-324

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Chapter 6: Appendix 1. TRIPOD checklist

Section/Topic	n		Checklist Item	Line No.
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1-2
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	27-51
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	57-67
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	69-71
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	77-86
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	79

Participants	6a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	79-84
	6b	D;V	Describe eligibility criteria for participants.	78
	6c	D;V	Give details of treatments received, if relevant.	108-109, 112-115
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	90-92, 103-105
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	NA
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	98-115
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	NA
Sample size	8	D;V	Explain how the study size was arrived at.	NA
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	122-123
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	126-128
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	126, 129-132
	10c	V	For validation, describe how the predictions were calculated.	135-139
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	132-135

	0e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	128-129
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	NA
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	NA
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Figure 1
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Table 1
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Table 1
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	Table 1
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	Suppl. Figure 2
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Figure 2
	15b	D	Explain how to the use the prediction model.	Figure 4

Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	161-163 (AUC)
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	NA
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	217-227
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	208-215
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	172-181
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	234-239
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	NA
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	242-244

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

Chapter 5: Appendix 1. STROBE checklist

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Line No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	28-32
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	32-39
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	48-61
Objectives	3	State specific objectives, including any prespecified hypotheses	63-67
Methods			
Study design	4	Present key elements of study design early in the paper	97-103
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	72-78

Participants	6	(b) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	79-89
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	95-121
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	95-121
Bias	9	Describe any efforts to address potential sources of bias	136-140
Study size	10	Explain how the study size was arrived at	NA

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	132-136
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	127-131
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	139-140
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	102-103
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Table 1
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Table 2
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Lines 157-162 Table 3, Table 4
		(*b*) Report category boundaries when continuous variables were categorized	Table 1, Table 2

	(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	176-182
Discussion			
Key results	18	Summarise key results with reference to study objectives	190-210
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	292-308
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	212-290
Generalisability	21	Discuss the generalisability (external validity) of the study results	292-304
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	322-324

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Chapter 6: Appendix 1. TRIPOD checklist

Section/Topic	m		Checklist Item	Line No.
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1-2
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	27-51
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	57-67
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	69-71
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	77-86
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	79
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	79-84
	5b	D;V	Describe eligibility criteria for participants.	78
	5c	D;V	Give details of treatments received, if relevant.	108-109, 112-115

Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	90-92, 103-105
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	NA
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	98-115
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	NA
Sample size	8	D;V	Explain how the study size was arrived at.	NA
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	122-123
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	126-128
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	126, 129-132
	10c	V	For validation, describe how the predictions were calculated.	135-139
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	132-135
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	128-129
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	NA
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	NA
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Figure 1

	3b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Table 1
	3c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Table 1
Model development	4a	D	Specify the number of participants and outcome events in each analysis.	Table 1
	4b	D	If done, report the unadjusted association between each candidate predictor and outcome.	Suppl. Figure 2
Model specification	5a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Figure 2
	5b	D	Explain how to the use the prediction model.	Figure 4
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	161-163 (AUC)
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	NA
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	217-227
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	208-215
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	172-181
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	234-239
Other information				

Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	NA
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	242-244

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

Chapter 7: Appendix 1. STROBE Checklist

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Line No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	28-30
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	30-44
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	55-64
Objectives	3	State specific objectives, including any prespecified hypotheses	65-69
Methods			
Study design	4	Present key elements of study design early in the paper	75-79
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	78-80

Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	81-85
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	86-95
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	99-111
Bias	9	Describe any efforts to address potential sources of bias	125-126
Study size	10	Explain how the study size was arrived at	NA

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	130-133
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	125-126
		(*b*) Describe any methods used to examine subgroups and interactions	135-136
		(*c*) Explain how missing data were addressed	`NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	117-119
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Table 1
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Table 5
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 6
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA

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Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	161-175
Discussion			
Key results	18	Summarise key results with reference to study objectives	179-188
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	236-244
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	195-234
Generalisability	21	Discuss the generalisability (external validity) of the study results	246-250
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	261-263

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Chapter 8: Appendix 1. STROBE Checklist

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Line No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	28-29
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	29-44
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	57-70
Objectives	3	State specific objectives, including any prespecified hypotheses	72-76
Methods			
Study design	4	Present key elements of study design early in the paper	81-85
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	84-88

Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	88-90
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	93-108
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	95-108
Bias	9	Describe any efforts to address potential sources of bias	120-122
Study size	10	Explain how the study size was arrived at	NA

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	114-118
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	120-124
		(*b*) Describe any methods used to examine subgroups and interactions	125-136
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Table 1
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Table 2, Table 3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Figure 2, Figure 3
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA

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Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	148-152, 157-161
Discussion			
Key results	18	Summarise key results with reference to study objectives	165-176
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	262-274
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	178-260
Generalisability	21	Discuss the generalisability (external validity) of the study results	266-267
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	283-285

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.