Use of routinely collected hospital data to explore access to and outcomes from different radiotherapy treatment strategies for locally advanced prostate cancer: national population-based studies

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DECLARATION

I, Matthew Parry, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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ABSTRACT

Background

The treatment of men with locally advanced prostate cancer is becoming increasingly complex with different treatment strategies available. Locally advanced prostate cancer is likely to harbour occult nodal metastases which requires local treatment of the prostate as well as treatment of the surrounding pelvic lymph nodes. The optimal management strategy is yet to be established but particular areas of interest include the use of additional pelvic lymph node irradiation and increasing the radiotherapy dose (through a brachytherapy boost). To date, there is little data about how different radiotherapy treatment strategies affect treatment-related toxicity and cancer outcomes, especially in the general population and outside the constraints of a clinical trial. This increasing complexity of prostate cancer management will also affect the organisation and delivery of cancer services in England, the impact of which is currently unknown.

Routinely collected hospital data has the benefit of being able to provide 'real-world' data for health services research and effectiveness studies. However, issues such as missing cancer stage data and the inability to accurately measure disease progression need to be appropriately addressed for any research affected by these issues to be considered robust.

This thesis aims to investigate treatments of patients with locally advanced prostate cancer using hospital data routinely collected in England's National Health Service.

Methods

Methodological development work explored ways to improve the completeness of cancer stage information and to measure disease progression (skeletal-related events) when using cancer registry, administrative hospital and radiotherapy data linked at patient level.

These datasets were also used to assess the impact of cancer service centralisation on how men with locally advanced prostate cancer are managed and to investigate treatment-related toxicity and cancer outcomes after different radiotherapy treatment strategies. Toxicity was measured according to the need for a procedural intervention, as identified through administrative hospital data, and using results from the National Prostate Cancer Audit patient-reported outcome survey. This patient survey was mailed out to men at least 18 months after diagnosis and included the Expanded Prostate Cancer Index Composite 26-item version, a validated instrument to measure functional outcomes in men with prostate cancer, and the EuroQol, which describes generic health-related quality of life. Cancer outcomes included skeletal-related events, as identified in administrative hospital data and radiotherapy data (developed earlier), and prostate cancer-specific mortality, as identified from official death records.

Results

The methodological development work established and validated methods to improve the completeness of prostate cancer stage data and to identify the occurrence of skeletal-related events in routinely collected hospital data.

The hospital where a man was diagnosed with locally advanced prostate cancer was not associated with whether or not he received radical treatment, but the use of surgery or a brachytherapy boost was more common if that treatment modality was available locally.

Additional irradiation of the pelvic lymph nodes was not associated with worse treatment-related toxicity. However, adding a brachytherapy boost to radiotherapy was shown to be detrimental for these outcomes, especially a low-dose rate brachytherapy boost which was also associated with increased gastrointestinal toxicity. A high-dose rate brachytherapy boost was found to improve cancer outcomes compared to radiotherapy only but low patient numbers prevented any definitive conclusion with respect to a low-dose rate brachytherapy boost.

Conclusions

Improvements of methods for handling missing data and identifying cancer progression can overcome some of the limitations of using routinely collected hospital data. I demonstrated that routinely collected hospital data can be used to study the impact of local radiotherapy service provision on the treatment that patients receive, and to compare treatment-related toxicity and cancer outcomes in patients receiving different radiotherapy treatment strategies.

I conclude that additional pelvic lymph node irradiation may not lead to worse toxicity and should be considered in locally advanced prostate cancer. In addition, if a brachytherapy boost is considered, a high-dose rate is preferable over a low-dose rate given its lower rate of gastrointestinal toxicity and its better cancer control compared to radiotherapy only.

Taken together, these results can be used to help improve radiotherapy service provision and treatment selection, especially with regards to additional lymph node irradiation and a brachytherapy boost.

LIST OF ABBREVIATIONS

AUA	American Urological Association
EAU	European Association of Urology
EBRT	External Beam Radiation Therapy
EBRT-BB	External Beam Radiation Therapy with Brachytherapy Boost
EPIC-26	Expanded Prostate Cancer Index Composite 26-item version
EQ	EuroQol
GI	Gastrointestinal
GU	Genitourinary
HQIP	Healthcare Quality Improvement Partnership
HDR	High-Dose Rate
HDR-BB	High-Dose Rate Brachytherapy Boost
HES	Hospital Episode Statistics
ICD-10	International Classification of Diseases, 10th Edition
IMD	Index of Multiple Deprivation
IMRT	Intensity Modulated Radiation Therapy
LDR	Low-Dose Rate
LDR-BB	Low-Dose Rate Brachytherapy Boost
MDT	Multi-Disciplinary Team

NHS	National Health Service
NCCN	National Comprehensive Cancer Network
NCRAS	National Cancer Registration and Analysis Service
NCRD	National Cancer Registry Data
NICE	National Institute for Health and Care Excellence
NPCA	National Prostate Cancer Audit on England and Wales
ONS	Office for National Statistics
OPCS-4	Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, 4th Revision
PO	Prostate Only
PPLN	Prostate and Pelvic Lymph Nodes
PROM	Patient-Reported Outcome Measure
PSA	Prostate-Specific Antigen
RCT	Randomised Controlled Trial
RTDS	Radiation Therapy Data Set
SEER	Surveillance, Epidemiology and End Results
SRE	Skeletal-Related Events
TNM	Tumour, Nodes, Metastasis
UK	United Kingdom

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1 INTRODUCTION

1.1 Locally Advanced Prostate Cancer

Prostate cancer is the most frequently diagnosed cancer and the second most common cause of cancer-related death in the United Kingdom (UK). Over 46,000 men are diagnosed with prostate cancer in the UK leading to over 11,000 deaths annually (1) and approximately one third of men with prostate cancer have locally advanced disease at diagnosis (2, 3).

Locally advanced disease includes men with either T3/4 disease or nodal metastases and between 10% and 40% of these men die within five years (4). Although high-risk localised disease has not technically spread outside of the prostate it is likely to progress if left untreated and may already include distant microscopic metastases at diagnosis. For this reason, the National Institute for Health and Care Excellence (NICE) guidelines include high-risk localised prostate cancer in the definition of locally advanced prostate cancer and hereafter we refer to these together as 'locally advanced' prostate cancer, unless otherwise specified.

The main focus of this thesis is on locally advanced prostate cancer because it represents men with potentially curable disease which requires the treatment of both the prostate and any potentially involved lymph nodes. The treatment strategies available are associated with varying oncological outcomes and treatment-related toxicity for which there is limited 'real-world' data for.

1.2 Routinely Collected Hospital Data

1.2.1 Overview

Routinely collected hospital data are collected without the primary intention of research but for surveillance or administrative purposes (5). Within the National Health Service (NHS) there are many examples of these data sources including cancer registries, Hospital Episode Statistics (HES) – an administrative hospital database of hospital admissions in England – and the radiotherapy data set (RTDS) which collects accurate radiotherapy information on dosage and fractionation. Given the national coverage of the NHS in England these datasets can provide a unique opportunity to report patterns of 'real-world' practice, the quality of cancer care delivery and outcomes achieved in routine clinical practice. It has already been shown that genitourinary (GU) and gastrointestinal (GI) toxicity following radiotherapy can be identified using hospital administrative data in England (6, 7) and worldwide (8-10), and therefore these measures can be used to compare different radiotherapy treatment strategies with respect to treatment-related toxicity.

In addition, these datasets allow for assessments to be made on a national scale in England with generalisable results to the whole population. Routine data sources in other countries are often fragmented with limited coverage. An example being in the US where data coverage of the Surveillance, Epidemiology and End Results (SEER) program only provides coverage for 35% of the population (11).

The national coverage of routinely collected data within the NHS also means that the population included is not restricted by any inclusion criteria which often limits the external validity of the findings from randomised controlled trials (RCTs) (12). RCTs are the gold standard for measuring the efficacy and short-term toxicity of a specific

intervention but often only include younger men who are reasonably fit. The outcomes reported therefore may not be generalisable to a national population (13). 'Real-world' data therefore allows for an assessment of treatment effectiveness in non-selected populations. Furthermore they can provide information on late toxicities, rare events and long-term outcomes which is not always possible from RCTs given they are not usually powered for such comparisons and the duration of follow up is often insufficient.

'Real-world' data is also being used for national audit purposes in order to compare providers and provide clinical benchmarking. The National Prostate Cancer Audit (NPCA) of England and Wales commenced prospective data collection in 2014 in order to compare providers of prostate cancer services with respect to service delivery, service organisation and clinical outcomes (14). The Clinical Outcomes Publication is an NHS England initiative and is an example of how audit and administrative data from 27 National Clinical Audits (including the NPCA) are being used to publish quality measures and drive quality improvement nationally (15).

1.2.2 Limitations

Cancer registry and administrative hospital data provide a vast source of cancer-specific information (16). These data are used extensively in population-based studies to investigate nationwide trends in cancer diagnosis and management (16-18), and enable assessments of treatment effectiveness in non-selected cancer patient populations. However, they are not without their limitations. When cancer-specific information is not known, or simply not recorded, a patient's cancer stage often cannot be determined. This is potentially problematic when these data are being used

for the purposes of research and health service evaluation, especially when staging greatly affects prognosis and clinical management (16, 19, 20).

In many countries, completeness of cancer registry data is improving over time but there is still a reliance on historical data, which are important in studying long-term outcomes and survival trends in prostate cancer (21, 22). The omission of patients with incomplete data from analyses may introduce significant selection bias and will lead to loss of statistical power.

Statistical methods, such as multiple imputation, are often used when dealing with missing data. These techniques replace missing values based on the patterns present in other variables within the sample (17, 23-27). However, staging data is often missing in certain clinical situations. For example, in prostate cancer registration, missing results for nodal involvement or distant metastases are more likely to represent negative results (N0 and M0, respectively) rather than positive results (N1 and M1, respectively). This is a consequence of two factors: first, the staging practice, as patients with low- or intermediate-risk prostate cancer may not have further staging investigations and second, record keeping, as negative results are less likely to be recorded than positive results. Given this pattern of missingness, imputation based on specific 'clinical assumptions' rather than statistical imputation provides an alternative approach to improve the completeness of prostate cancer staging information.

Further to this, national or regional cancer registries are highly effective at identifying patients who have been diagnosed with cancer but they often fail to recognise patients whose cancer has progressed or recurred. In contrast, cancer trials often use progression and recurrence as key endpoints but this is problematic for trials of prostate cancer (and other cancers with a favourable prognosis), when these events

occur late in the course of the disease. This highlights the need for further methodological development work into how prostate cancer and recurrence can be measured using routinely collected hospital data.

One such marker of progression in prostate cancer is the occurrence of skeletal-related events and administrative hospital data from the United States and Denmark have been used successfully to measure this outcome (28-33). These encompass pathological fractures, spinal cord compression, radiotherapy for bone metastases, or bone surgery. This highlights the possibility of using this measured event as a marker of disease progression or recurrence, allowing for an observation of the true natural history of prostate cancer, and as a clinically important event in its own right.

The limitations highlighted above will provide the basis for the methodological development work of this thesis in order to improve the data completeness and to develop a measure of disease progression. This will allow for subsequent effectiveness studies of different radiotherapy treatment strategies and also for an assessment of treatment access.

1.3 Management of Locally Advanced Prostate Cancer

1.3.1 Overview

External beam radiotherapy (EBRT) and androgen deprivation therapy remains the standard of care for locally advanced prostate cancer, but practices of care continue to evolve (34). For example, two major questions in this area are whether to include the pelvic lymph nodes within the radiation fields to treat any potential nodal metastases, or to increase the radiation dose to the prostate by combining external beam radiotherapy with a brachytherapy boost (EBRT-BB). Radiotherapy treatment

strategies like these have the primary goal of achieving better cancer control, reducing the likelihood of disease progression and ultimately, premature death (34, 35). However, it is important that such gains in oncological outcomes do not come at the expense of a significant increase in treatment-related toxicity.

The treatment-related toxicity of radiotherapy is well documented, whereby the term 'toxicity' encompasses the range of adverse events and post-treatment complications. However, toxicity can be measured in many different ways using clinician-reporting, patient-reporting and routinely collected hospital data. To date clinical grading scales, such as the Common Terminology Criteria of Adverse Events (CTCAE) and the Radiation Therapy Oncology Group (RTOG), have been the mainstay for reporting radiotherapy-related toxicity. Studies using patient-reported outcome measures (PROMs) are needed because clinical measures based on clinician-reporting or administrative hospital data do not always fully capture the outcomes that are relevant to patients (10). It has also been shown that PROMs report higher rates of toxicity symptoms than clinician-reporting and emphasises their importance (36).

1.3.2 Pelvic Lymph Node Irradiation

One particular area of interest for radiotherapy in prostate cancer is with respect to irradiating the prostate and pelvic lymph nodes (PPLN) instead of the prostate-only (PO). In the UK, NICE currently recommend PPLN-EBRT for patients with a high risk of nodal involvement (37) whereby a second definition for 'high-risk' is defined as a Roach score greater than 15% based on PSA and Gleason score (38).

Data from retrospective studies have demonstrated varying results regarding the benefit of PPLN-EBRT versus PO-EBRT, and all RCTs to date have been negative with regard to biochemical disease-free survival and overall survival (39-43). However,

several shortcomings of these trials have been highlighted as potential reasons why no differences in outcome were observed. Such limitations were the inclusion of low-risk men, inadequate coverage of all pelvic lymph nodes (up to the L5-S1 interface) and differences in hormone duration (40, 41, 43). Results from two RCTs using intensity modulated radiation therapy (IMRT) are awaited to confirm the definitive role of PPLN-EBRT (44, 45).

It is well documented that radiotherapy for prostate cancer can lead to gastrointestinal (GI) and/or genitourinary (GU) complications but there are mixed results regarding whether PPLN-EBRT, and subsequently the treatment of a large volume of normal tissue, confers worse toxicity. Studies to date have been small scale with low numbers of men and, until recently, IMRT was not used (39, 41, 43, 46-49). As IMRT is now the accepted standard for prostate radiotherapy, data on the efficacy and toxicity following 3D-conformal radiotherapy is difficult to contextualise (50).

Very few studies have commented on toxicity rates in this area and most are from an era when lower doses of EBRT were used. Two of the three RCTs commented on toxicity rates and used the approved RTOG toxicity scoring scale. The RTOG 9413 trial showed that PPLN-EBRT was associated with an increase in grade 1 GI and GU toxicity, but only an increase in late GI toxicity when considering grade 3 (severe) toxicity (41, 49). The genitourinary group (GETUG) 01 trial showed inconclusive results where the observed increase in grade 1 GI toxicity with PPLN-EBRT proved to be non-significant. Interestingly, GETUG 01 showed an increased rate of severe acute GU toxicity for PO-EBRT but relate this to the higher EBRT dose per fraction delivered to the prostate (≥2 Gy vs. 1.80 Gy) (43).

A handful of cohort studies have also looked into toxicity rates, generally showing that PPLN-EBRT was well tolerated and that late severe toxicity was rare. Even with older techniques, Mantini et al. (47) failed to find any difference in toxicity rates between the two groups. The study of Aizer et al. (39) was the first to include IMRT but this was only used to treat the prostate. A four-field technique was used for the pelvic lymph nodes as prior data had suggested that IMRT did not improve lymph node coverage (51). This may go some way to explaining the increased rate of acute GI toxicity (grade 2 or worse) found with pelvic lymph node irradiation, plus the fact that the significance level was only borderline (p=0.048) (39).

Initial reports of PPLN-EBRT using IMRT have been encouraging with no acute or late severe toxicity (52, 53). Studies using PPLN-IMRT doses up to 60 Gy (54) further indicate its safety and tolerability where only a small increase in GI toxicity was observed, compared to men undergoing PO-IMRT from the CHHip phase III trial (55) and the systematic review of Holch et al. (56), and all but grade 1 GI side effects had resolved by 18 weeks.

The GETUG 01 trial was the only RCT to report quality of life and toxicity using patient-reported outcome measures (PROMs). The study found no significant difference between cohorts but there was no assessment of bowel function and baseline scores were not balanced (43). The second study used lower doses than those used currently and was a prospective matched-pair cohort study using the Expanded Prostate Cancer Index Composite 26-item version (EPIC-26) questionnaire and allowed for an assessment of all symptom domains. In contrast to the GETUG 01 trial, baseline scores were comparable and bowel domains appeared to deteriorate further in the acute phase for the PPLN-EBRT group. Bowel function improved for the PO-EBRT group

in the late phase, almost to baseline, however a slight deterioration remained for the PPLN-EBRT group (48).

Lilleby et al. (46) conducted the first cohort study of PPLN-EBRT using IMRT, however this was in addition to conformal EBRT to the prostate. They indicated an improvement in late adverse effects when better conformal techniques were used to treat the whole pelvis. They also found that although bowel function and bother deteriorated during the acute phase, as was shown with the matched-pair analysis above, the situation had considerably improved by one-year post-treatment compared to baseline. This was also the case for urinary function and bother. Data from case series have indicated that PPLN-IMRT can be as tolerated as PO-IMRT where quality of life remains almost unchanged at 6, 12 and 24 months post treatment, compared to baseline (52).

Data from case series and phase II studies have shown that PPLN-IMRT is safe and tolerable but there is no published data comparing EBRT, with and without pelvic lymph node irradiation, using solely modern techniques (i.e. IMRT). The worse toxicity from using outdated techniques maybe guiding its limited use in modern day practice. Further investigation is warranted because if toxicity is shown to be comparable then its use would be better supported and encouraged, in line with current guidelines (53, 54).

1.3.3 Brachytherapy Boost

Brachytherapy boost, in combination with EBRT (EBRT-BB), has also been investigated as a method of increasing the dose of radiation delivered to the prostate. Brachytherapy is a form of radiotherapy where a sealed radiation source is placed directly inside the prostate and is given as permanent low-dose rate (LDR) seed

implantation or as temporary high-dose rate (HDR) brachytherapy. As dose optimisation is performed after placement of catheters, HDR enables more consistent target coverage than permanent seed implants, which allows for greater dose conformity, and lower doses to normal tissues (urethra and rectum) (57). The high degree of conformity achievable and rapid dose fall off outside the target volume makes HDR brachytherapy a particularly attractive method of increasing the radiation dose. This is particularly important when considering the role of a brachytherapy boost for men at high risk of disease progression.

There have been three trials which have assessed the efficacy of a brachytherapy boost (two using LDR-BB and one using HDR-BB) (58-63). The trials using HDR-BB and LDR-BB (temporary Iridium-192 wires) were carried out prior to higher radiation doses being used routinely, with the control EBRT only arm essentially receiving outdated doses of radiotherapy (55 Gy and 66 Gy) from outdated techniques (4 field or 3D conformal) (58, 61-63). Both studies found that combined treatment significantly improved biochemical survival however, no difference was observed for overall survival, even after a median follow-up of 14 years, in the follow-up study of Hoskin et al (59, 60). The ASCENDE-RT trial is the only level 1 evidence in support of EBRT-BB (permanent Iodine-125 seeds) which used current EBRT doses and found that men receiving LDR-BB were twice as likely to be free of biochemical failure after a median follow-up of 6.5 years. However, there was no comparison on prostate-cancer specific mortality or overall survival (62).

A systematic review, published in 2009, combining observational data concluded that HDR-BB results in superior biochemical control and overall survival than EBRT only or LDR-BB (64). A recent cohort study of very high-risk men (Gleason score 9-10) has

demonstrated, for the first time, that EBRT-BB was associated with a longer time to distant metastases and better prostate cancer-specific mortality compared to a radical prostatectomy or EBRT only (65).

Only two studies have previously reported PROMs to compare the toxicity of EBRT-BB versus EBRT only (66, 67), of which only one represented contemporary patients who received exclusively IMRT (66). A single-centre, retrospective cohort study of 870 consecutive patients, published in 2013, compared 470 men who received high-dose IMRT (86.4 Gy) with 400 men who received EBRT (40-50.4 Gy) and either HDR-BB or LDR-BB. The International Index of Erectile Function was used to assess sexual function and there was no significant difference between EBRT-BB and EBRT only. Importantly, no other functional domains were reported (66). Although differences in sexual function were found to be statistically significant in our larger study, these did not reach clinical significance.

Of the three RCTs to use EBRT-BB (58-63, 67) within the experimental arm, only one reported on health-related quality of life (67). Published in 2013, the study included 218 patients to compare an HDR-BB with EBRT only and used the Functional Assessment of Cancer Therapy (FACT) questionnaire. There was no difference, over the 10.5 year follow-up, between treatment arms and no evidence that the scores were changing over time or different to pre-treatment baseline levels. Importantly, a specific question of 'ability to maintain an erection' was selected to calculate an erection function score. Mean scores were found to be consistently lower in the HDR-BB group, but differences proved insignificant after correction for multiple comparisons. Mean scores throughout follow-up were significantly lower than pre-treatment scores for HDR-BB but not for EBRT only, although it was not possible to

translate whether this conferred a clinically relevant decline. The reasons for these lower scores was unclear but the authors suggest the lack of a formal assessment of sexual function as a potential cause. One question from the FACT survey was used to this end instead of a formal assessment such as the International Erectile Function Score (67).

Clinician-reported toxicity is more frequently reported in the literature than PROMs. Results from the RCTs of HDR-BB and LDR-BB (temporary Iridum-192 wires) indicate that acute and late GU toxicity (grade ≥2, Dische scoring method and grade ≥3, National Cancer Institute of Canada Clinical Trials Group Expanded Common Toxicity Criteria) were comparable between the brachytherapy boost and EBRT only groups (59-61). However, the ASCENDE-RT trial of 398 patients, showed that LDR-BB (permanent Iodine-125 seeds) was associated with higher acute and late GU morbidity (grade ≥2, LENT-SOMA scale) up to 5 years of follow-up (63).

Only one observational trial of 287 men has directly compared men receiving HDR-BB and LDR-BB with respect to toxicity. LDR-BB was associated with worse GI toxicity (at least grade 3) compared to HDR-BB (cumulative incidence 8% and 4%, respectively). However, differences did not reach statistical significance (68).

Observational data of an EBRT cohort and a mixed brachytherapy boost cohort (both HDR-BB and LDR-BB) highlights that although a brachytherapy boost confers initially worse acute GU toxicity (grade ≥2) the majority is only transient (66, 69). However, in terms of late GU toxicity, HDR-BB has also been associated with a ten-fold increase in the occurrence of urethral strictures compared to EBRT only (70). More recent observations have shown that improvements in imaging software have been able to better protect the urethra against the development of strictures following an

HDR-BB (69). Data from the most contemporary patients, who received IMRT, have shown a higher incidence of acute GU toxicity after an HDR-BB or LDR-BB (grade ≥2, Common Terminology Criteria for Adverse Events) but toxicity at 7 years was comparable and so indicating toxicity resolution (66).

With regards to GI toxicity, one of the HDR-BB trials found rectal discharge to be more prevalent in the EBRT only group up until 12 weeks after treatment (59). This is supported by observational studies showing worse acute, but also late, GI toxicity for men receiving EBRT only (69, 71, 72). In addition to the higher radiotherapy doses used for the men receiving EBRT only, it is likely that the older techniques used in these studies (3D conformal radiotherapy) were also contributing to the higher rates of GI toxicity. For example, men receiving a higher dose of IMRT (86.4 Gy) in the EBRT only arm in one study, did not experience worse acute GI toxicity (grade ≥2, Common Terminology Criteria for Adverse Events) compared to the brachytherapy boost cohort (66). To add further contrast, the ASCENDE-RT trial observed a non-significant trend towards worse GI morbidity after an LDR-BB (grade ≥2, LENT-SOMA scale) further highlighting the different toxicity profiles of each type of brachytherapy boost (63).

There is growing evidence in support of multimodal treatment using brachytherapy for prostate cancer. However, the combined effect on adverse events needs to be appropriately investigated. Larger studies using contemporary EBRT techniques are needed, particularly those using PROMs. If shown to be tolerable for men with prostate cancer this will aid the continued uptake of this modality at additional centres throughout the country. Further to this, confirmation from an RCT that improved biochemical control translates into a survival advantage over EBRT only is required before this can become standard of care. PIVOTALboost is a multicentre

phase III RCT which is currently recruiting with the primary objective of assessing whether pelvic lymph node radiotherapy with or without an HDR brachytherapy boost leads to improved failure free survival (73).

1.4 Centralisation of Cancer Services

For over a decade, specialist radiotherapy and surgical services for prostate cancer have been centralised in England, which has restricted the number of centres providing these specialist services and in turn increased the centres' average volume of procedures. The rationale for this centralisation is to optimise the quality of care men receive and to improve patient outcomes by focussing treatment in high-volume centres (74, 75). To co-ordinate access to these specialist services 48 specialist Multi-Disciplinary Teams (MDT) were set up across England. Each specialist MDT is made up of a regional referral network of hospitals within a specific geographical area of the country. Hospitals assigned as the lead of each regional referral network, or 'hub' site, act as regional co-ordinating centres. Each hub is usually a specialist centre for either radiotherapy, surgery or both and the other hospitals within the network act as 'spoke' hospitals. Most spoke hospitals are non-specialist centres and therefore have to refer to specialist centres for radical treatment, but a few spoke hospitals provide one or more treatment modalities on-site.

The NPCA collect information regarding the organisation of prostate cancer services for each regional referral network and the specialist treatment services available on-site at each hospital (76). Between April 2014 and March 2016, 138 hospitals in the English NHS provided diagnostic facilities for prostate cancer, of which 53 were specialist surgical centres, 51 were specialist radiotherapy centres and 19 were specialist HDR brachytherapy centres. Access to radiotherapy and surgical

centres is available to every hospital within England via one of the 48 regional referral networks. However, HDR brachytherapy services are only available to hospitals within 24 of these regions, either directly or externally via a neighbouring regional referral network. HDR brachytherapy has therefore become a super-specialised treatment modality within the complex, centralised system for prostate cancer care in England. LDR brachytherapy boost is used even less frequently in England with only two centres using it to any significant degree.

The hub-and-spoke model for prostate cancer care aims to improve outcomes while aiming to guarantee appropriate access, irrespective of the hospital where a patient is diagnosed. Despite this, studies have started to emerge highlighting that this centralisation process has led to an inequity of access to surgery in the treatment of other cancers, such as lung cancer and liver metastases in colorectal cancer (76-78). To date there is no data investigating this for prostate cancer services in England.

2 RESEARCH DESIGN

2.1 Overview

Treatment decisions for men with locally advanced prostate cancer are particularly complex. My research design attempts to address the complexity of these clinical decisions using the scale and depth of routinely collected hospital data and is therefore divided into three components: methodological development work, health services research and effectiveness studies. National cancer registry data, administrative hospital data, radiotherapy data, audit survey data, PROMs and mortality data, all linked at patient-level where appropriate, are used to assess the impact of this increasing complexity on the organisation and delivery of cancer

services, and in turn the treatments that men receive and the treatment-related toxicity they experience.

2.2 Aim

To use linked routinely collected hospital data to explore access to, and the effectiveness of, different radiotherapy treatment strategies for men with locally advanced prostate cancer.

2.3 Objectives

In order to achieve my study aim my objectives were divided into three components: methodological development work, health services research and effectiveness studies.

2.3.1 Methodological Development Work

Objective 1 (Research Paper 1): To explore whether missing prostate cancer stage can be imputed using specific clinical assumptions.

Objective 2 (Research Paper 2): To develop and validate an approach to identify skeletal-related events in men with prostate cancer using routinely collected data.

2.3.2 Health Services Research

Objective 3 (Research Paper 3): To explore how centralisation affects the radical treatment of locally advanced prostate cancer.

2.3.3 Effectiveness Studies

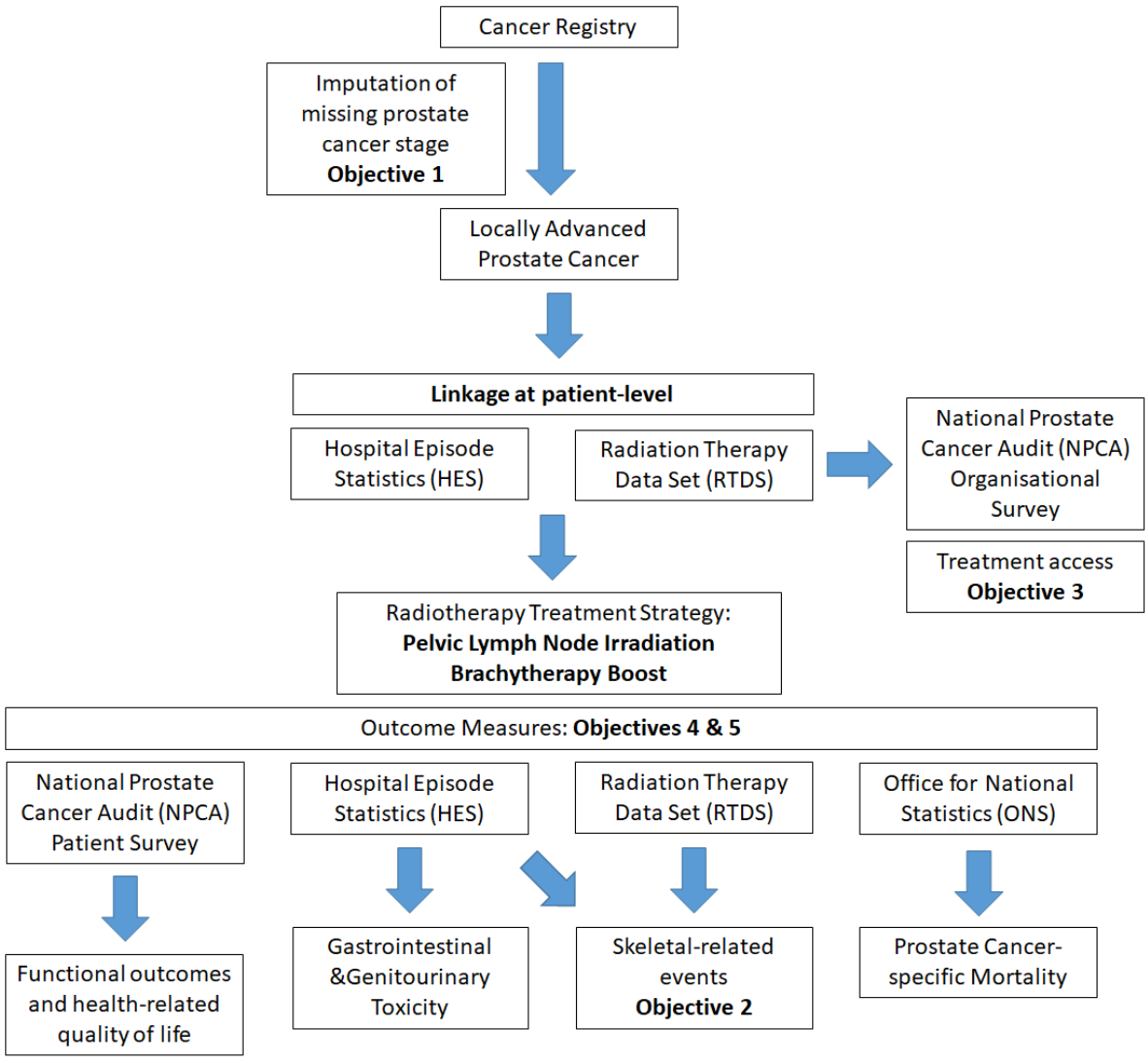
Objective 4 (Research Paper 4 & 5): To investigate whether pelvic lymph node irradiation, in addition to prostate-only radiotherapy, affects medium-term outcomes in men receiving primary radiotherapy for their prostate cancer.

Objective 5 (Research Paper 6 & 7): To investigate whether brachytherapy boost, in addition to primary radiotherapy, affects medium-term outcomes in men with prostate cancer.

2.4 Data Sources

The NPCA works with the National Cancer Registration and Analysis Service (NCRAS), Public Health England as a data collection partner in England. NCRAS collects patient-level data from all NHS acute providers and from a range of national data-feeds. **Figure 1** shows how the data sources were linked and how they were used according to each objective.

Figure 1. Flowchart of data sources.



2.4.1 National Cancer Registry Data (NCRD)

NCRD is a merged dataset of cancer-specific data, originally collected by the eight English cancer registries since 1990, and recently combined into a national cancer registry (79). This dataset supplies the information necessary for prostate cancer staging based on their TNM classification and Gleason score. This dataset also provides demographic information (socio-economic deprivation, age and ethnicity). Socio-economic deprivation will be measured using the Index of Multiple Deprivation (IMD). The data completeness of the NCRD is high for some core fields, with 98% of patients having a valid NHS number ensuring high case ascertainment and national representation.

2.4.2 National Prostate Cancer Audit (NPCA)

The NPCA is a national clinical audit commissioned by the Healthcare Quality Improvement Partnership (HQIP) in response to the need for better information about the quality of services and care provided to patients with prostate cancer in England and Wales. Prospective data collection began in 2014 including the collection of PROMs to measure functional outcomes and health-related quality of life after radical treatment. Patient surveys were mailed to men diagnosed with prostate cancer between April 1, 2014 and September 30, 2016 who received radical local treatment within 18 months of their prostate cancer diagnosis. Two reminders were sent to non-responders 3 and 6 weeks after the initial mailing.

The questionnaire included the Expanded Prostate Cancer Index Composite 26-item version (EPIC-26) which is a validated instrument for measuring quality of life related to prostate cancer according to five domains (urinary incontinence, urinary irritation/obstruction, sexual function, bowel function and hormonal disturbance) (80).

Each domain contains between 4-7 items and scores were summarised for each domain on a scale of 0 to 100, with higher scores representing better function. A recent systematic review supports the use of EPIC-26 for longitudinal studies and these PROMs will provide valuable information about the toxicity of different radiotherapy treatment strategies (81).

The questionnaire also included the EuroQol (EQ-5D-5L) which describes generic HRQoL based on five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Responses to these domains had five levels of severity ("no problems", "slight problems", "moderate problems", "severe problems" and "unable to/extreme problems"). An index score (0 – "death"; 1 – "perfect health") was calculated by matching the pattern of the five responses to a set of utilities from the general UK population (82).

As baseline EPIC-26 and EQ-5D-5L scores were not collected, the patient survey included three questions which asked patients to recall urinary, sexual and bowel function at the time of diagnosis. These recalled measures were captured on a 5-point scale from "no problem" to "large problem".

In 2014, the NPCA undertook an organisational survey of all NHS hospitals across England. Questionnaires established the availability and location of core diagnostic, treatment and support services for the management of non-metastatic prostate cancer. The survey has been updated annually to reflect changing service organisation. This organisational survey was used to provide information about available services at each hospital with regards to radical prostatectomy, EBRT and

brachytherapy, as well as other services. These survey results allowed for an assessment of how service provision impacted on the treatments men received.

2.4.3 National Radiotherapy Data Set (RTDS)

The collection of radiotherapy data through the RTDS has been mandated since April 2009 and collects information regarding every patient receiving radiotherapy and/or brachytherapy across all NHS hospitals in England. The purpose of the RTDS is to collect consistent data and provide nationally comparable data to inform planning, provision and commissioning of radiotherapy services across the NHS (83). This database has previously been linked to the NPCA dataset with good linkage rates (>95%) and provides accurate, up-to-date information on radiotherapy episodes within the NHS.

The RTDS collects information on radiotherapy doses and fractions, anatomical site (prostate, prostate and pelvic lymph nodes or non-primary site metastases), treatment dates and NHS hospital. This dataset provides more detailed information than other routine data sources of radiotherapy information, such as SEER in the US, which allows for the allocation of treatment groups and the subsequent comparisons of different radiotherapy treatment strategies with respect to treatment-related toxicity and cancer outcomes.

2.4.4 Hospital Episode Statistics (HES)

The HES Admitted Patient Care dataset is an administrative hospital database used for payment by results at NHS healthcare providers according to a standard national tariff. HES provides inpatient information on diagnoses, procedures/operations, length of stay and readmissions at NHS hospitals in England (84). HES has been successfully linked to the NCRD and the NPCA with good linkage

rates (~95%). The NPCA indicators, derived from linked HES data, will be used to identify severe gastrointestinal and genitourinary toxicity (6, 85).

2.4.5 Office for National Statistics (ONS)

ONS provides the information on the date of death and the cause of death. This allows for the calculation of prostate cancer-specific mortality. ONS has been successfully linked to the NCRD with very high linkage rates (>95%).

2.5 Study Design

Research Paper 1: "Imputation of missing prostate cancer stage in English cancer registry data based on clinical assumptions" - *See Chapter 3*

The **first** research paper (objective 1) was a methodological study exploring whether missing prostate cancer stage could be imputed using specific clinical assumptions. Kaplan Meir analysis was used to compare 4-year overall survival in men with missing and complete staging items according to specific clinical assumptions. Multivariable Cox regression was used to explore survival time according to each of the clinical assumptions. The clinical imputation method was compared with that of multiple imputation by chained equations. This study was essential so the clinical assumptions could improve the risk stratification of men with prostate cancer for the subsequent research papers.

Research Paper 2: "Identifying skeletal-related events for prostate cancer patients in routinely collected hospital data" - *See Chapter 4*

The **second** research paper (objective 2) was a methodological study to develop a coding framework in data available in the NPCA to identify skeletal-related events in routinely collected hospital data. The framework was then validated firstly by assessing

how often skeletal-related events occurred with a diagnosis code for bone metastasis, secondly by estimating the 5-year cumulative incidence of skeletal-related events according to prostate cancer stage at the time of diagnosis, and thirdly by comparing the incidence of skeletal-related events observed with our coding framework against results of other studies. This study was important to be able to measure skeletal-related events in order to compare treatment combinations in Chapter 7.

Research Paper 3: "Impact of cancer service centralisation on the radical treatment of men with high-risk and locally advanced prostate cancer: a national cross-sectional analysis in England" - *See Chapter 5*

The **third** research paper (objective 3) analysed the impact of cancer service centralisation (hub-and-spoke model) on access to radical treatment, and on the specific type of radical treatment that men with high-risk and locally advanced prostate cancer receive. Multivariable multilevel Poisson regression was used to estimate the risk ratio of receiving radical treatment by whether men were diagnosed at a hub or spoke hospital. A second regression model was performed for a cohort of men who received radical treatment to estimate the likelihood of receiving a radical prostatectomy according to whether surgery was available on-site at the diagnosing hospital. A final regression model was performed for a cohort of men who received radiotherapy to estimate the likelihood of receiving HDR-BB according to whether these services were regionally available.

Research Paper 4: "Treatment-related toxicity using prostate-only versus prostate and pelvic lymph node intensity-modulated radiation therapy: a national population-based study" - *See Chapter 6*

The **fourth** research paper (objective 4) investigated whether PPLN-IMRT affects treatment-related toxicity in men receiving primary radiotherapy for their prostate cancer compared to PO-IMRT. In 2017, the NPCA validated two performance indicators which can identify severe GU and GI toxicity following radiotherapy from hospital administrative data (6, 7). GI or GU toxicity was defined as the presence of both an International Classification of Diseases, 10th Edition (ICD-10) diagnostic code and an Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, 4th Revision (OPCS-4) code in a patient's HES record which were related to complications after radiotherapy. This is comparable to at least grade 2 toxicity according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (86). These indicators were used to assess the outcomes of PPLN irradiation and allow for the quantification of the complications that can be expected.

Research Paper 5: "Toxicity of pelvic lymph node irradiation with intensity modulated radiation therapy for high-risk and locally advanced prostate cancer: a national population-based study using patient-reported outcomes" - *See Chapter 7*

The **fifth** research paper (also objective 4) investigated whether irradiation of the pelvic lymph nodes, in addition to prostate-only radiotherapy, affects patient-reported outcomes in men receiving primary radiotherapy for their prostate cancer. Functional outcomes and quality-of-life measures capture outcomes that are directly relevant to patients. As such, PROMs have an important role to play in the evaluation of treatment harms and benefits (81). So far, use of PROMs with regard to locally

advanced prostate cancer is lacking and, given the unavoidable toxicity of additionally irradiating the pelvic lymph nodes, a full assessment is warranted. The NPCA collects PROMs on all men receiving radical treatment 18 months after diagnosis so that the impact of treatments on disease-specific functional outcomes and quality-of-life can be measured (3).

The questionnaire used for the PROMs was designed by the NPCA Project Team following review of current literature/guidelines and in consultation with clinical and patient representatives in the Audit's Clinical Reference Group. The questionnaire includes:

- The EPIC-26 – a validated instrument to measure prostate cancer related quality of life in five domains (urinary incontinence, urinary irritation/obstruction, bowel function, sexual function, hormonal disturbance).
- The EuroQol (EQ)-5D-5L – a generic validated PROM that describes health related quality of life in five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).

Research Paper 6: "Impact of high-dose rate and low-dose rate brachytherapy boost on toxicity, functional and cancer outcomes in patients receiving external beam radiation therapy for prostate cancer: a national population-based study" - *See Chapter 8*

The **sixth** research paper (objective 5) investigated whether brachytherapy boost, in addition to primary radiotherapy, affects toxicity in men with prostate cancer. The same performance indicators as Research Paper 4 (6, 7) were used to assess the outcomes in this specific multimodal setting and allow for the quantification of the complications that can be expected. Additional indicators for skeletal-related

events and prostate cancer-specific mortality were also used to assess cancer-specific outcomes.

Research Paper 7: "Patient-reported outcomes following external beam radiation therapy for prostate cancer with and without a high-dose rate brachytherapy boost: a national population-based study" - *See Chapter 9*

The **seventh** research paper (also objective 5) investigated whether HDR-BB in addition to primary radiotherapy, affects patient-reported outcomes in men with prostate cancer. The same PROMs as Research Paper 5 were used to assess the outcomes in this specific multimodal setting and allow for the quantification of the complications that can be expected (3).

2.6 Ethics

The NPCA Project Team has access to all the national databases needed for this study through its data collection partner NCRAS. I only had access to fully anonymised patient data and therefore my research was exempt from UK National Research Ethics Committee approval. My PhD has been reviewed by the London School of Hygiene and Tropical Medicine's Research Ethics Committee.

2.7 Patient & Public Involvement

Locally advanced prostate cancer represents the men at high-risk of progression and the men for which aggressive treatment is the most important (34). Factors which affect treatment selection need to be explored nationally so that any inequity of access to different treatment strategies can be addressed. Prostate cancer services have been centralised to improve patient outcomes but this may be negatively impacting on treatment access for patients diagnosed at non-specialist units. The

NPCA is already providing feedback to NHS providers regarding prostate cancer care but as more follow-up data are collected the scope for improving service provision will continue.

The Clinical Reference Group of the NPCA was continuously involved in the development of the audit and advised on its future direction. There was patient and public representation in the Clinical Reference Group from Prostate Cancer UK and Tackle Prostate Cancer, who ensured that patients' input was implemented at every stage of my PhD. Engagement with patient representatives demonstrated that my research was needed, was relevant to patients and was focussed towards their needs. Ensuring equity of treatment access and improving patient outcomes in locally advanced disease are particular priorities of these charities, and helped inform my research questions. Both charities supported this PhD throughout and provided guidance from the patients' perspective, especially with the interpretation of the results and the dissemination of the findings to patients and the public.

3 MISSING STAGING DATA

3.1 Research Paper 1

Title: Imputation of missing prostate cancer stage in English cancer registry data based on clinical assumptions.

The online PDF version can be accessed at:

https://www.sciencedirect.com/science/article/abs/pii/S1877782118304077?via%3Dihub

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	LSH1800100	**Title**	Dr
First Name(s)	Matthew		
Surname/Family Name	Parry		
Thesis Title	Use of routinely collected hospital data to explore access to and outcomes from different radiotherapy treatment strategies for locally advanced prostate cancer: national population-based studies.		
Primary Supervisor	Professor Jan van der Meulen		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Cancer Epidemiology		
When was the work published?	18/11/18		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/A		
Have you retained the copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

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Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Designed the work, analysed and interpreted the data, drafted the article and approved the final version to be published.

SECTION E

Student Signature	M. Parry
Date	8/1/21

Supervisor Signature	J. van der Meulen
Date	8/1/21

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Imputation of missing prostate cancer stage in English cancer registry data based on clinical assumptions

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ABSTRACT

Background: Cancer stage can be missing in national cancer registry records. We explored whether missing prostate cancer stage can be imputed using specific clinical assumptions.

Methods: Prostate cancer patients diagnosed between 2010 and 2013 were identified in English cancer registry data and linked to administrative hospital and mortality data (n = 139,807). Missing staging items were imputed based on specific assumptions: men with recorded N-stage but missing M-stage have no distant metastases (M0); low/intermediate-risk men with missing N- and/or M-stage have no nodal disease (N0) or metastases; and high-risk men with missing M-stage have no metastases. We tested these clinical assumptions by comparing 4-year survival in men with the same recorded and imputed cancer stage. Multi-variable Cox regression was used to test the validity of the clinical assumptions and multiple imputation.

Results: Survival was similar for men with recorded N-stage but missing M-stage and corresponding men with M0 (89.5% vs 89.6%); for low/intermediate-risk men with missing M-stage and corresponding men with M0 (92.0% vs 93.1%); and for low/intermediate-risk men with missing N-stage and corresponding men with N0 (90.9% vs 93.7%). However, survival was different for high-risk men with missing M-stage and corresponding men with M0. Imputation based on clinical imputation performs as well as statistical multiple imputation.

Conclusion: Specific clinical assumptions can be used to impute missing information on nodal involvement and distant metastases in some patients with prostate cancer.

1. Introduction

As prostate cancer is biologically heterogeneous, it is important to differentiate clinically between indolent, low-risk disease that is localised to the prostate and disease that is highly aggressive and likely to metastasise [1]. Management options for non-metastatic disease differ significantly depending on the clinical stage and grade of disease, ranging from active surveillance to radical local treatment (with or without supplementary systemic therapy). Patients presenting with distant metastases are managed differently with systemic and palliative treatments taking precedence [2].

Cancer registry and administrative hospital data provide a vast source of cancer-specific information [3]. These data are used extensively in population-based studies to investigate nationwide trends in cancer diagnosis and management [3–5]. When prostate cancer-specific information is not known, or simply not recorded, a patient's cancer stage often cannot be determined. This is potentially problematic when these data are being used for the purposes of research and

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health service evaluation, especially when staging greatly affects prognosis and clinical management [3,6,7].

In many countries completeness of cancer registry data is improving over time but there is still a reliance on historical data, which are important in studying long-term outcomes and survival trends in prostate cancer [8,9]. The necessary omission of patients with incomplete data from analyses may introduce significant selection bias and will lead to loss of statistical power.

Statistical methods, such as multiple imputation, are often used when dealing with missing data. These techniques re-classify missing values based on the patterns present in other variables within the sample. [4,10–14]. Staging data is often missing in certain clinical situations. For example, in prostate cancer registration, negative results for nodal involvement (N0) or distant metastases (M0) may be more likely to be missing than positive results (N1 and M1, respectively). This is a consequence of two factors: first, the staging practice, as patients with low/intermediate-risk prostate cancer may not have further staging investigations and second, record keeping, as negative results are less likely to be recorded than positive results.

Given this pattern of missingness, imputation based on specific 'clinical assumptions' rather than statistical imputation provides an alternative approach to improve the completeness of prostate cancer staging information. For example, prostate cancer patients with tumour stage T1 and a Gleason score of six are unlikely to undergo staging investigations because the likelihood they have nodal involvement or distant metastases is very low. For these patients, one can assume that the missing N- and M-stage are N0 and M0, respectively. Similar assumptions can be made for patients who have complete data for nodal status but missing data for distant metastases. If staging data is available for nodal disease, it is likely that staging was also performed to look for distant metastases but the negative result was not recorded. The likelihood of missing M-stage representing positive disease is therefore very low and missing M-stage can be assumed to be M0.

Specific clinical assumptions may therefore be used to impute missing staging items in cancer registry data in a systematic way in order to risk stratify more men with prostate cancer. We explored to what extent staging data completeness can be improved by using the following four clinical assumptions:

1 Men with a recorded N-stage but missing M-stage have no distant metastases (M0).
2 Low/intermediate-risk men with missing M-stage have no distant metastases (M0).
3 Low/intermediate-risk men with missing N-stage have no nodal disease (N0).
4 High-risk men with missing M-stage have no distant metastases (M0).

An assumption for high-risk men and missing N-stage was not assessed given that for the majority of research and evaluation purposes these men will be already assigned to the locally advanced group as a minimum.

2. Material and methods

All patients who were diagnosed with prostate cancer between January 1st 2010 and December 31st 2013 were identified in the English cancer registry using the ICD-10 code 'C61' [15]. Data collected by the eight regional English cancer registries have been combined into a national data set. This was then linked at patient-level to Hospital Episode Statistics (HES), an administrative database of all hospital admissions in the English National Health Service and data from the Office for National Statistics (ONS), giving 139,807 patients over this time period. Follow-up was available to 31st December 2014. Data collected from the English cancer registry included age, Gleason score, and T-, N- and M-stages (TNM). TNM data used preferentially clinical cancer registry items and then pathological cancer registry items, in line with the Union for International Cancer Control (UICC) TNM 7th edition, taking staging information that was updated as much as possible by cancer registry staff.

Table 1
Staging criteria used for prostate cancer according to the National Prostate Cancer Audit without clinical imputation.

Prostate Cancer Stage	Staging Criteria
Advanced	M1
Locally Advanced	(≥T3 or GS ≥8 or N1) + M0
Localised	≤T2 + GS ≤7 + N0 + M0
Unknown Stage	None of the above

The Royal College of Surgeons (RCS) Charlson score was used to identify co-morbid conditions from the HES records based on previously coded co-morbidity within one year of their prostate cancer diagnosis [16]. Socio-economic deprivation was derived from the Index of Multiple Deprivation (IMD, The English Indices of Deprivation, 2012). The IMD ranks 32,482 areas in the country and patients are grouped into socioeconomic quintiles based on the national distribution.

Men were labelled as 'complete' if their prostate cancer could be clinically categorised into localised, locally advanced or advanced disease (Table 1). Low/intermediate-risk, non-metastatic prostate cancer was defined as T1 or T2 and Gleason score ≤7 in the absence of nodal or distant metastases. High-risk prostate cancer was defined as any one of T3, T4, N1 or Gleason score ≥8 in the absence of distant metastases (M0). According to the National Prostate Cancer Audit [17] and the National Institute for Health and Care Excellence [2] risk stratification, high-risk localised disease was classified as 'locally advanced' disease. PSA was not available in the English cancer registry prior to 2014 and so was not used. Patients with missing data items were only considered to have a missing stage if there was insufficient data elsewhere to clinically stage their disease. For example, a patient with documented metastases (M1) can be staged as advanced, irrespective of the completeness of the other stratification variables. Staging completeness was stratified by year of diagnosis, age, RCS Charlson score and socio-economic deprivation.

Kaplan Meier analysis was used to compare 4-year overall survival in men with missing and complete staging items according to each of our clinical assumptions (see above). Patient survival was displayed with corresponding 95% confidence intervals to compare survival in patients with complete and imputed staging data. The log-rank test was used to test differences between survival curves at a p-value of 0.05. To be consistent with each clinical assumption we expect that:

1 Men with missing M-stage or M0 will have similar survival if the patient has a recorded N-stage.
2 Low/intermediate-risk men with missing M-stage or M0 will have similar survival.
3 Low/intermediate-risk men with missing N-stage or N0 will have similar survival.
4 High-risk men with missing M-stage or M0 will have similar survival.

'X' values in the English cancer registry represent when N- and M-stage information was either inconclusive or missing (NX and MX, respectively). In this analysis, we used NX and MX to represent missing values.

Multi-variable Cox regression was used to explore survival time according to each of the clinical assumptions, adjusting for age, RCS Charlson score, socio-economic deprivation, year of diagnosis and the eight English cancer registry regions displaying hazard ratios (HRs) and 95% confidence intervals (CIs). We then compared this clinical imputation method with that of multiple imputation by chained

Table 2
Completeness of prostate cancer staging with and without clinical imputation.

			Staging completeness						
			Without assumptions				With assumptions		
	N	%	Metastatic n (%)	Locally advanced n (%)	Localised n (%)	Missing n (%)	Locally advanced n (%)	Localised n (%)	Missing n (%)
Total	139,807	100	13,257 (9.5)	24,889 (17.8)	22,341 (16.0)	79,320 (56.7)	27,899 (20.0)	39,960 (28.6)	58,691 (42.0)
Year of diagnosis									
2010	33,701	24.1	2009 (6.0)	2845 (8.4)	841 (2.5)	28,006 (83.1)	3589 (10.7)	4544 (13.5)	23,559 (69.9)
2011	33,463	23.9	2361 (7.1)	4354 (13.0)	2089 (6.2)	24,659 (73.7)	5283 (15.8)	6355 (19.0)	19,464 (58.2)
2012	35,225	25.2	4370 (12.4)	8130 (23.1)	8239 (24.4)	14,486 (41.1)	8741 (24.8)	12,677 (36.0)	9437 (26.8)
2013	37,418	26.8	4517 (12.1)	9560 (25.6)	11,172 (29.9)	12,169 (32.5)	10,286 (27.5)	16,384 (43.8)	6231 (16.7)
Age group (yrs)									
≤60	15,321	11.0	856 (5.6)	2375 (15.5)	3571 (23.3)	8519 (55.6)	2822 (18.4)	6151 (40.2)	5492 (35.9)
60–69	47,923	34.3	3136 (6.5)	8972 (18.7)	9661 (20.2)	26,154 (54.6)	10,341 (21.6)	16,783 (35.0)	17,663 (36.9)
70–79	51,063	36.5	4740 (9.3)	10,102 (19.8)	7904 (15.5)	28,317 (55.5)	11,093 (21.7)	14,049 (27.5)	21,181 (41.5)
80–89	22,435	16.1	3819 (17.0)	3.184 (14.2)	1187 (5.3)	14,245 (63.5)	3371 (15.0)	2907 (13.0)	12,338 (55.0)
≥90	3065	2.2	706 (23.0)	256 (8.4)	18 (0.6)	2085 (68.0)	272 (8.9)	70 (2.3)	2017 (65.8)
Number of co-morbidities (RCS Charlson score)									
0	109,470	78.3	8256 (7.5)	20,469 (18.7)	18,530 (16.9)	62,215 (56.8)	23,011 (21.0)	33,062 (30.2)	45,141 (41.2)
1	21,007	15.0	2961 (14.1)	3285 (15.6)	2987 (14.2)	11,774 (56.1)	3642 (17.3)	5285 (25.2)	9119 (43.4)
> 2	9330	6.7	2040 (21.9)	1135 (12.2)	824 (8.8)	5331 (57.1)	1246 (13.4)	1613 (17.3)	4431 (47.5)
Socio-economic deprivation									
1 (least deprived)	34,259	24.5	2863 (8.4)	5683 (16.6)	5560 (16.2)	20,153 (58.8)	6546 (19.1)	10,532 (30.7)	14,318 (41.8)
2	33,669	24.1	3082 (9.2)	6145 (18.3)	5410 (16.1)	19,032 (56.5)	6860 (20.4)	9961 (29.6)	13,766 (40.9)
3	29,533	21.1	2945 (10.0)	5426 (18.4)	4578 (15.5)	16,584 (56.2)	6060 (20.5)	8311 (28.1)	12,217 (41.4)
4	23,462	16.8	2357 (10.1)	4184 (17.8)	3735 (15.9)	13,186 (56.2)	4625 (19.7)	6354 (27.1)	10,126 (43.2)
5 (most deprived)	18,884	13.5	2010 (10.6)	3451 (18.3)	3058 (16.2)	10,365 (54.9)	3808 (20.2)	4802 (25.4)	8264 (43.8)

equations. Ten complete data sets were created taking account of age, RCS Charlson score, socio-economic deprivation, diagnosis year, T-stage and Gleason score [18]. For the groups of patients defined by each clinical assumption we determined how often missing N and M stages were assigned to be N0 or N1 and M0 or M1 by averaging the proportions of patients with these specific imputed staging results over the ten data sets. We also used Cox regression analysis to calculate separately specific hazard ratios for patients for whom the statistical imputation had assigned N0 or N1 for patients with missing N stage and M0 or M1 for patients with missing M stage. The hazard ratios for these specific imputed results were combined using Rubin's rules.

3. Results

A total of 139,807 men with a diagnosis of prostate cancer in the English cancer registry could be linked to the HES database (January 1st 2010–December 31st 2013) and 43% of the patients could be staged accurately. Completeness and variation of clinical staging is shown in Table 2. Completeness increased with year of diagnosis, from 17% in 2010 to 68% in 2013. Completeness was similar for all age groups below 80 years (43%–45%) and decreased for those aged between 80–90 years (37%) and > 90 years (32%). As socio-economic deprivation increased, data completeness improved slightly from 41% to 45% but the presence of co-morbidity did not appear to affect completeness.

When we explored the validity of imputations of missing N-stage or M-stage based on our four clinical assumptions we found the following results. First, 4-year overall survival was very similar for men with a recorded N-stage, but missing M-stage, and corresponding men with recorded M0 (89.5% vs 89.6%). This similarity was observed to such a degree that the patient survival curves for MX and M0 appear as one line. Survival of men with M1 in this cohort was substantially lower at 39.7% (Fig. 1). This pattern was also observed when the analysis was restricted to N0 and N1 disease individually.

Second, for low/intermediate-risk men with missing M-stage and corresponding men with recorded M0, survival was also very similar (92.0% vs 93.1%), and substantially higher than men with recorded M1 (59.2%). Again, this similarity was observed to such a degree that the patient survival curves for MX and M0 appear as one line (Fig. 2a).

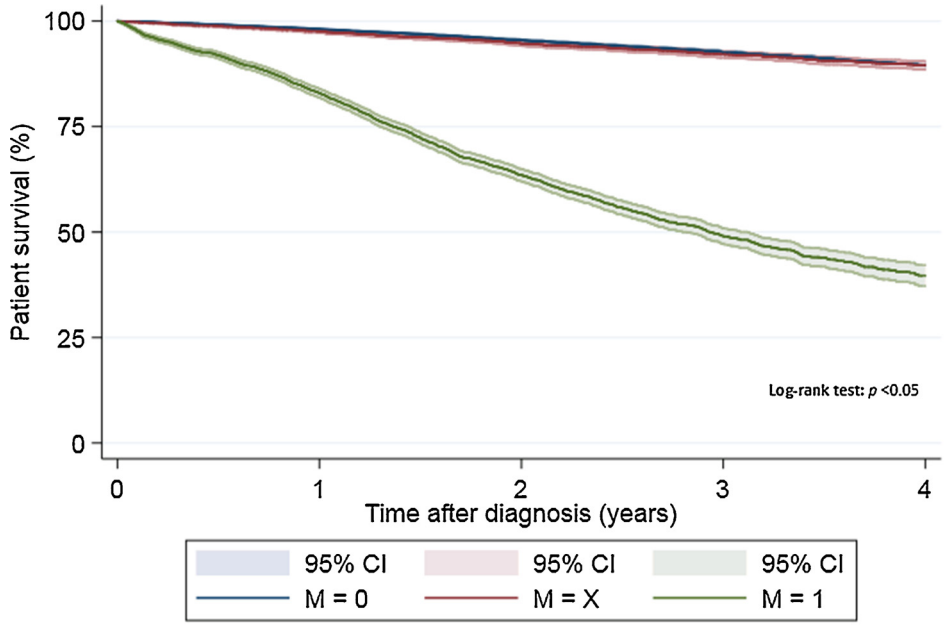
Third, the same pattern was seen for low/intermediate-risk men with missing N-stage and corresponding men with recorded N0 (90.9% vs 93.7%), where survival was also much lower for men with N1 (81.4%, Fig. 2b).

Fourth, 4-year survival for high-risk men with missing M-stage was 71.4% which differed substantially from corresponding men with recorded M0 or M1 (84.5% vs 36.7%, Fig. 3). These results support the first three clinical assumptions that:

1 Recorded N-stage: missing M-stage → M0
2 Low/Intermediate-risk men: missing M-stage → M0
3 Low/Intermediate-risk men: missing N-stage → N0

Assumptions two and three therefore assume that any man with both missing N-stage and missing M-stage are N0 and M0. The fourth clinical assumption was not supported, thus missing M-stage cannot be imputed to M0 in high-risk men. All the 95% confidence intervals presented with the survival curves were narrow around the survival estimates, highlighting the precision of our results and appropriateness of our assumptions. When we used these three clinical assumptions to impute missing N-stage and M-stage, we could increase staging completeness from 43% to 58% by allocating an extra 20,629 patients to an appropriate stage over the four year time frame (2010–2013). For the most recent data only (2013), completeness rose from 68% (without assumptions) to 83% (with assumptions).

Adjusted Cox regression, compared to the unadjusted analysis, showed that there was some residual bias when using the first three clinical assumptions as there were significant differences in survival between MX (assumption one and three) or NX (assumption two) compared to either N0 or M0, respectively (HRs and 95% CIs > 1) (Table 3). The adjusted model provided further support for assumption two as it showed a decrease from an unadjusted HR of 1.50 to an adjusted HR of 1.26, confirming the presence of confounding from other



***Note:** Patient survival for men with M0 (blue line) or MX (red line) was very similar with narrow and overlapping confidence intervals (95%). Both lines therefore appear superimposed.

Fig. 1. Overall survival for men with complete N-stage (N1/N0) showing the distribution of M-stage (M1/M0/missing M).

variables.

However, the performance of our clinical assumptions compared to multiple imputation is very similar. For assumptions two and three, survival of NX and MX values imputed to N0 and M0 using multiple imputation were in line with our clinical assumptions given the very similar hazard ratios (Tables 3 and 4). Multiple imputation rarely imputes values to M1 (assumption two) or N1 (assumption three), highlighting that our clinical assumptions are as appropriate as multiple imputation in this setting and both methods perform relatively well for patients in the low/intermediate-risk group. For assumption one, our clinical assumptions were weaker than the method using multiple imputation given the hazard ratios for the MX values imputed to M0 were further away from 0 (HR 1.39 95% 1.27–1.53 vs. HR 1.13 95% CI 1.00–1.28). However multiple imputation was still imperfect as those missing values imputed to M1, rather than M0, were not comparable to the survival of men with M1 (HR 2.53 95% CI 2.07–3.09 vs. 7.11 95% CI 6.71–7.53), a bias which does not affect our clinical assumptions given they are assumed to be negative (M0).

4. Discussion

4.1. Overview

Imputation based on specific clinical assumptions increased the completeness of clinical staging from 43% to 58% for prostate cancer patients recorded in the English cancer registry between 2010 and 2013. We found that overall survival of patients with available N- or M-stage were similar to those with imputed results based on three of the four clinical assumptions, thus providing evidence for their validity. These clinical assumptions perform as well as multiple imputation and are more easily applicable at local hospitals for those without appropriate statistical software or expertise.

4.2. Other national databases

Staging completeness is variable between national data sets in Europe, Australasia and the US [8,9,19–24]. The National Prostate Cancer Registry of Sweden reports staging completeness at 97% when using the National Comprehensive Cancer Network (NCCN) risk classification. This represents the highest level of any national data set and uses Gleason score and PSA as well as TNM—a success which is likely to be attributed to cancer registration being compulsory and mandated in law [25]. A further European cancer registry in Denmark reports staging completeness at 71% (2004–2009) restricting classification to TNM [9]. The Australasian databases have published completeness at 58% and 27% in New South Wales, Australia (1999–2007) [8] and New Zealand (2006–2008) [19], respectively, according to the SEER summary stage.

Completeness of tumour variables in the US SEER database, using Medicare patients, is reported at 67% (2004–2006) and is unique by using a detailed D'Amico risk stratification which utilises all of PSA, Gleason and a sub-classification of T2 [22]. T2(a–c) describes the proportion of the prostate affected and provides an additional variable for quantifying risk. Whatever risk stratification is being used, this overview of completeness in national databases indicates that in most countries approaches that are similar to the one that we present in this paper may be used to increase staging completeness of cancer registry data.

4.3. Alternative approaches for dealing with missing staging data

Missing N- and M-stage data is usually dealt with by reclassifying them to N0 and M0. The National Prostate Cancer Registry of Sweden uses a modified version of the NCCN classification and in doing so assumes that men labelled 'not N1' or 'not M1' are N0 and M0, respectively. As we have shown, we could not assume that high-risk men are free from nodal and/or distant metastases. With only 3% of men being unstaged in the Swedish cancer registry, it is unlikely that this approach will have led to substantial biased staging profiles but it may be less appropriate for use in countries that have cancer registries with less complete staging data. In addition, the modified NCCN classification uses PSA to classify regional and distant metastases (≥ 50 and > 100,

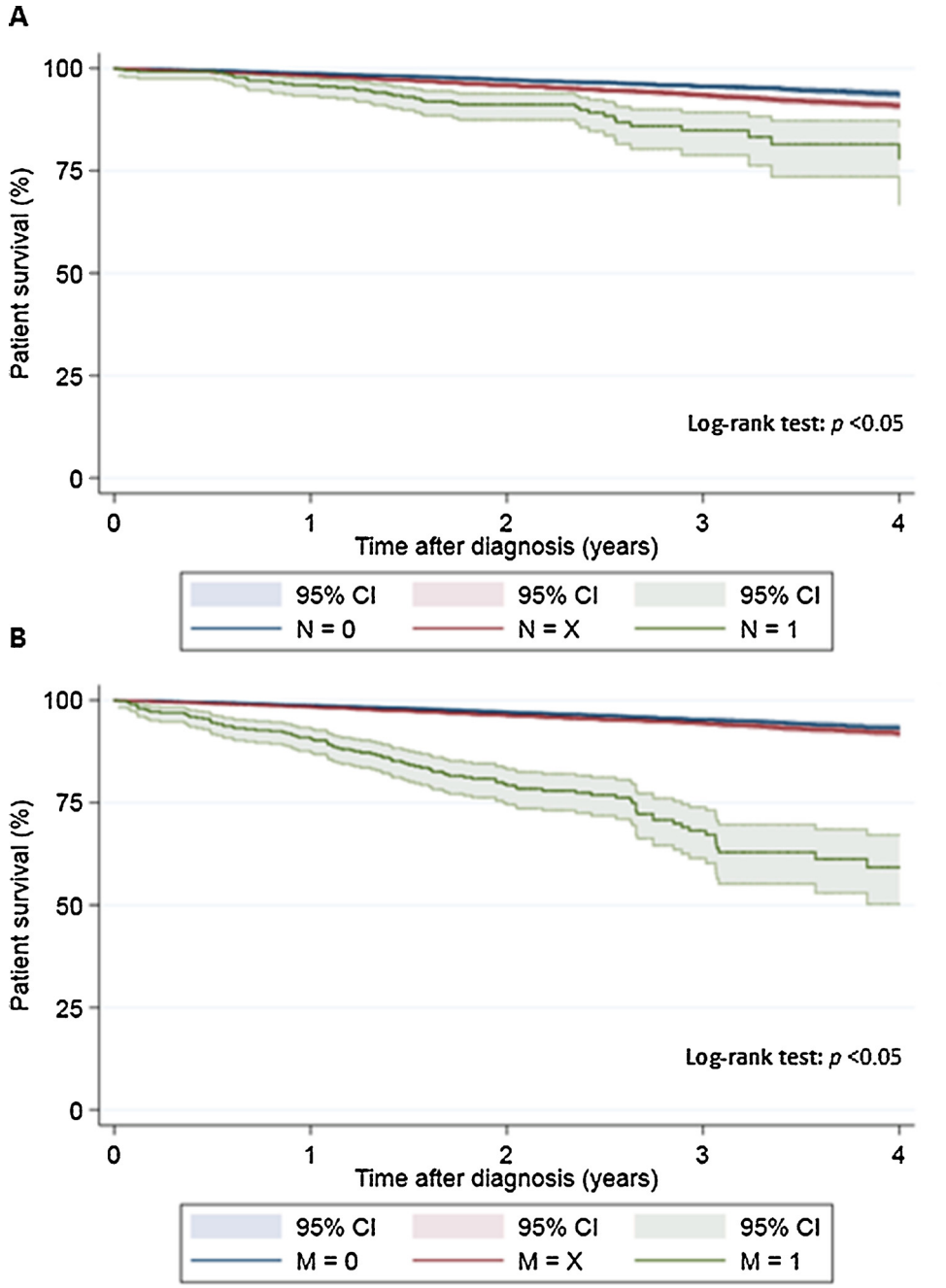


Fig. 2. Overall survival for men with low/intermediate-risk disease (T1-2 and Gleason score ≤7) showing the distribution of: a. M-stage (M1/M0/missing M) b. N-stage (N1/N0/missing N).

respectively) which may prevent the understaging of missing N- and M-stage in Swedish men [24].

A study of the completeness of T, N and M in the Danish cancer registry used an approach which has similarities with the one that we present in this study. The Danish approach led to the staging of 70.5% by assuming that men with tumour stage T1 or 2 and missing N- and M-stage had localised disease, which implies that they assumed these men had N-stage N0 and M-stage M0 [9]. This is very similar to our approach but we were able to include Gleason score in our staging method and validate our assumptions by comparing survival estimates in men with complete and imputed missing staging data.

An Australian population-based cohort study, linked with cancer registry data, concluded that multiple imputation can provide valid estimates for missing staging data but they indicated that caution should be used when applying their methods to other data sets [13]. An important element of their imputation method was that it also used information on the primary treatment that patients received in the first six months after diagnosis, although even without treatment

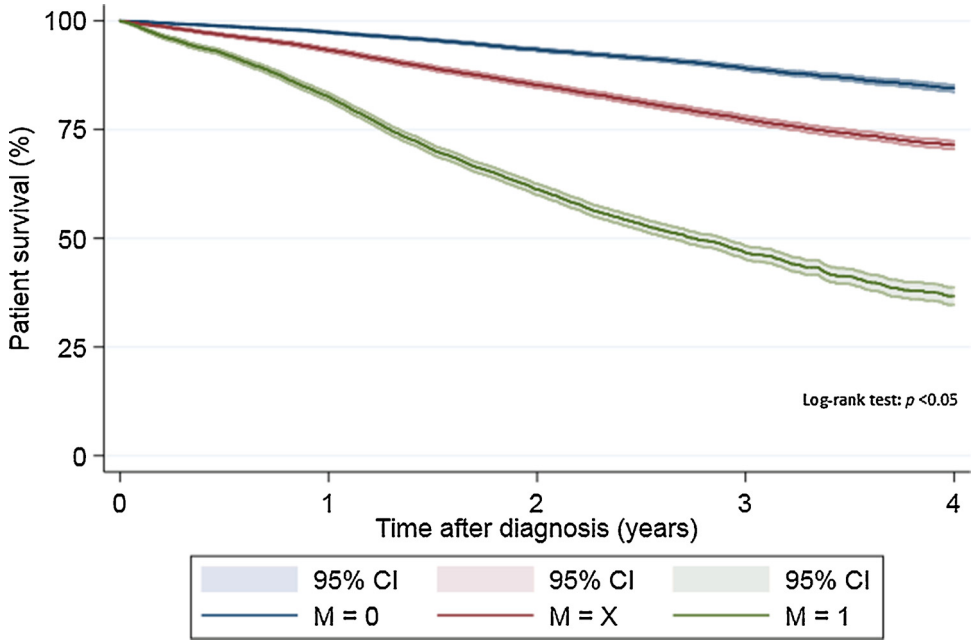


Fig. 3. Overall survival for men with high-risk disease (T3-4 or Gleason score ≥8) showing the distribution of M-stage (M1/M0/missing M).

information included, multiple imputation appears to provide valid estimates.

4.4. Characteristics of incomplete data

Characteristics of men with incomplete prostate cancer staging information have not been previously described using the English cancer registry. Consistent with previous literature, completeness of clinical staging of prostate cancer decreases with increasing age. Other studies have also shown that co-morbidity and socio-economic deprivation is associated with missing data but our data does not support this [9,19–21,26–28]. For the very elderly, the likelihood of undergoing staging investigations is low given their diminished life expectancy. It has also been shown that cancer staging is more often incomplete in patients with cancer types that have a poor survival, although this has not been shown for prostate cancer [21].

Staging investigations are especially valuable for men who are candidates for curative treatment. For this reason it is important to rule out metastatic disease in high-risk men, with systemic imaging, to ensure that radical local treatment is indicated. Therefore, men with low-risk disease are unlikely to undergo these staging investigations given that metastases are unlikely. This is supported in the 2014 NICE guidance where men with low-risk disease should not be routinely offered bone scans [2]. Men with intermediate-risk prostate cancer may undergo a bone scan but again, the likelihood of this being positive is low and negative results are more likely to be missing than positive ones. Our specific clinical assumptions follow these clinical patterns and so we imputed missing N- and M-stage data only in low/intermediate-risk men. Our approach is supported by a study of Swedish cancer registry data which showed that men with incomplete staging tended to be of low- or intermediate-risk [24].

4.5. Strengths and limitations

Strengths of this population-based study include the high volume of patients included (139,807). English cancer registry data includes all NHS hospitals in England which ensures that our findings are nationally generalisable. Second, we used a validated method to identify co-morbidity data in linked hospital administrative data which provided reliable identification of co-morbidity [16].

An important limitation of our staging algorithm is that we did not have access to PSA data in our patient group and we could not sub-classify tumour stage T2 into T2a, T2b or T2c. As a result, we could not use the full D'Amico classification [29]. PSA is now included in the data

Table 3
Results of Cox regression analysis for exploring the mortality of patients according to N-stage (N0/NX/N1) or M-stage (M0/MX/M1) for the patient cohorts applicable to clinical assumptions 1–3.

Clinical assumption	N (%)	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio[a] (95% CI)
1: Complete N-stage	66,576 (100)		
M0	54,788 (82.3)	1	1
MX	6950 (10.4)	1.08 (0.99–1.19)	1.39 (1.27–1.53)
M1	4838 (7.3)	9.40 (8.88–9.94)	7.07 (6.68–7.50)
2: Low/intermediate-risk	40,664 (100)		
N0	25,705 (63.2)	1	1
NX	14,594 (35.9)	1.50 (1.36–1.65)	1.26 (1.13–1.40)
N1	365 (0.9)	3.53 (2.57–4.85)	3.02 (2.20–4.16)
3: Low/intermediate-risk	40,664 (100)		
M0	25,247 (62.1)	1	1
MX	15,021 (13.9)	1.21 (1.10–1.34)	1.21 (1.09–1.34)
M1	396 (1.0)	7.77 (6.30–9.57)	5.40 (4.37–6.66)

[a] Adjusted for age, RCS Charlson score, socio-economic deprivation, year of diagnosis and English Cancer Registry region.

Table 4
Results of Cox regression analysis for exploring the mortality of patients according to N-stage (N0/NX/N1) or M-stage (M0/MX/M1) following the creation of 10 complete data sets using multiple imputation by chained equations for the patient cohorts defined by clinical assumptions 1–3.[a]

Clinical assumption	%	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio[b] (95% CI)
1: Complete N-stage	100		
M0	82.3	1	1
MX imputed to M0	9.1	0.85 (0.76–0.96)	1.13 (1.00–1.28)
MX imputed to M1	1.3	2.78 (2.30–3.35)	2.53 (2.07–3.09)
M1	7.3	9.40 (8.88–9.94)	7.11 (6.71–7.53)
2: Low/intermediate-risk	100		
N0	62.1	1	1
NX imputed to N0	35.1	1.48 (1.34–1.64)	1.25 (1.12–1.39)
NX imputed to N1	0.8	2.06 (1.16–3.64)	1.68 (0.96–2.94)
N1	0.9	3.53 (2.57–4.85)	3.03 (2.21–4.17)
3: Low/intermediate-risk	100		
M0	62.1	1	1
MX imputed to M0	35.6	1.18 (1.06–1.31)	1.20 (1.08–1.34)
MX imputed to M1	1.3	2.06 (1.24–3.43)	1.23 (0.75–2.04)
M1	1.0	7.77 (6.30–9.57)	5.41 (4.38–6.69)

[a] See the methods section for a further explanation of the multiple imputation method used and how the resultant ten data sets were combined for the Cox regression results.
[b] Adjusted for age, RCS Charlson score, socio-economic deprivation, year of diagnosis and English Cancer Registry region.

that is being recorded in the English cancer registry which will allow for a more accurate risk stratification [17].

4.6. Clinical implication

If missing staging data is not handled correctly, it can produce biased results. Our study validates the use of specific clinical assumptions to improve staging completeness so that subsequent work using cancer registry data is rendered more reliable. A key advantage of these assumptions over statistical methods is their simplicity and easy application. The clinical assumptions impute just one value for each missing N or M variable, whereas multiple imputation produces a distribution of values (across several data sets). This means that with our clinical rules local hospitals can summarise and analyse their data easily without the need for statistical software or expertise.

One could also use this method to account for missing data using clinically relevant information, followed by statistical imputation as a second step to account for the remainder. Although we have only shown this approach is as appropriate for prostate cancer it may also be applicable to other cancers such as breast, bladder or melanoma. Prostate cancer is unique in that full staging investigations are not always warranted, and treatment not always required, which may limit its use in other cancer types. Specific assumptions would need to be tailored to each cancer type given the differences in their diagnostic pathways.

5. Conclusions

National cancer registries are important data sources for research and healthcare service evaluation. How to handle missing data is therefore of particular importance as historic prostate cancer data are currently being used with relatively high rates of missing cancer stage. Our clinical imputation approach can be an important first step to improve the completeness of cancer stage data, prior to employing statistical imputation techniques, or if statistical methods are not feasible.

Appendix A

See Table A1.

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Author's contribution

M.G.P. designed the work, analysed and interpreted the data, drafted the article and approved the final version to be published. A.S. designed the work, analysed and interpreted the data, provided critical revision and approved the final version to be published. T.E.C. analysed and interpreted the data, provided critical revision and approved the final version to be published. S.C. analysed and interpreted the data, provided critical revision and approved the final version to be published. J.N. provided critical revision and approved the final version to be published. A.A. designed the work, analysed and interpreted the data, provided critical revision and approved the final version to be published. N.W.C. provided critical revision and approved the final version to be published. H.P. provided critical revision and approved the final version to be published. J.v.d.M. designed the work, analysed and interpreted the data, contributed to the drafting of the article, and approved the final version to be published.

Conflict of interest

J.v.d.M. reports a contract with the Healthcare Quality Improvement Partnership for the provision of the National Prostate Cancer Audit (www.npca.org.uk) funded by the Healthcare Quality Improvement Partnership (www.hqip.org.uk).

H.P. has attended and received honoraria for advisory boards, travel expenses to medical meetings, and served as a consultant for AstraZeneca, Astellas, Janssen, Sanofi Aventis, Takeda, Ipsen, Ferring, Sandoz, and Novartis.

N.W.C. has attended and received honoraria for advisory boards, travel expenses to medical meetings, and served as a consultant for AstraZeneca, Astellas, Bayer, Janssen, Sanofi Aventis, Takeda, Ipsen and Ferring.

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Table A1
Completeness of individual TNM staging items with and without clinical imputation.

			TNM completeness				
			Without assumptions			With assumptions	
	N	%	T n (%)	N n (%)	M n (%)	N n (%)	M n (%)
Total	139,807	100	95,745 (68.5)	66,576 (47.6)	75,218 (53.8)	81,170 (58.1)	93,909 (67.2)
Year of diagnosis							
2010	33,701	24.1	15,192 (45.1)	6976 (20.7)	8090 (26.4)	10,235 (30.4)	12,903 (38.3)
2011	33,463	23.9	20,099 (60.1)	12,836 (38.4)	13,696 (40.9)	16,401 (49.0)	18,754 (56.0)
2012	35,225	25.2	29,361 (83.4)	22,398 (63.6)	25,481 (72.3)	26,010 (73.8)	29,990 (85.1)
2013	37,418	26.8	31,093 (83.1)	24,366 (65.1)	27,132 (72.5)	28,523 (76.2)	32,262 (86.2)
Age group (yrs)							
≤60	15,321	11.0	11,808 (77.1)	8653 (56.5)	8213 (53.6)	10,606 (69.2)	11,165 (72.9)
60–69	47,923	34.3	36,296 (75.7)	26,815 (56.0)	26,789 (55.9)	32,435 (67.7)	34,799 (72.6)
70–79	51,063	36.5	35,189 (68.9)	24,612 (48.2)	28,154 (55.1)	29,941 (58.6)	34,400 (67.4)
80–89	22,435	16.1	11,514 (51.3)	6037 (26.9)	10,834 (48.2)	7673 (34.2)	12,257 (54.6)
≥90	3,065	2.2	938 (30.6)	459 (15.0)	1228 (40.1)	515 (16.8)	1288 (42.0)
Number of co-morbidities (RCS Charlson score)							
0	109,470	78.3	77,972 (71.2)	54,486 (49.8)	59,107 (53.4)	6644 (60.7)	74,637 (68.2)
1	21,007	15.0	13,087 (62.3)	9006 (42.9)	11,301 (53.8)	10,959 (52.2)	13,661 (65.0)
> 2	9330	6.7	4686 (50.2)	3084 (33.1)	4810 (51.6)	3767 (40.4)	5611 (60.1)
Socio-economic deprivation							
1 (least deprived)	34,259	24.5	23,772 (69.4)	15,947 (46.6)	17,686 (51.6)	20,082 (58.6)	22,983 (67.1)
2	33,669	24.1	23,683 (70.3)	16,271 (48.2)	18,383 (54.6)	20,040 (59.5)	23,100 (68.6)
3	29,533	21.1	20,458 (69.3)	14,269 (48.3)	16,244 (55.0)	17,381 (58.9)	20,183 (68.3)
4	23,462	16.8	15,533 (66.2)	11,018 (47.0)	12,608 (53.7)	13,181 (56.2)	15,363 (65.5)
5 (most deprived)	18,884	13.5	12,299 (65.1)	9071 (48.0)	10,297 (54.5)	10,486 (55.5)	12,280 (65.0)

References

[1] J. Shoag, C.E. Barbie, Clinical variability and molecular heterogeneity in prostate cancer, Asian J. Androl. 18 (4) (2016) 543–548.
[2] National Institute for Health and Care Excellence, Prostate Cancer: Diagnosis and Management, Available at: (2014) (Accessed 16 February 2018), http://www.nice.org.uk/guidance/CG175.
[3] M. Sogaard, M. Olsen, Quality of cancer registry data: completeness of TNM staging and potential implications, Clin. Epidemiol. 4 (Suppl. 2) (2012) 1–3.
[4] U. Nur, L.G. Shack, B. Rachet, J.R. Carpenter, M.P. Coleman, Modelling relative survival in the presence of incomplete data: a tutorial, Int. J. Epidemiol. 39 (1) (2010) 118–128.
[5] G. Gandaglia, F. Bray, M.R. Cooperberg, et al., Prostate cancer registries: current status and future directions, Eur. Urol. 25 (5) (2015) 979–986.
[6] S.H. Giordano, Y.F. Kuo, Z. Duan, G.N. Hortobagyi, J. Freeman, J.S. Goodwin, Limits of observational data in determining outcomes from cancer therapy, Cancer 112 (11) (2008) 2456–2466.
[7] D.F. Penson, P.C. Albertsen, Lessons learnt about early prostate cancer from large scale databases: population-based pearls of wisdom, Surg. Oncol. 11 (1–2) (2002) 3–11.
[8] Q. Luo, X.Q. Yu, C. Cooke-Yarborough, D.P. Smith, D.L. O'Connell, Characteristics of cases with unknown stage prostate cancer in a population-based cancer registry, Cancer Epidemiol. 37 (6) (2013) 813–819.
[9] M. Nguyen-Nielsen, T. Froslev, S. Friis, M. Borre, N. Harving, M. Sogaard, Completeness of prostate cancer staging in the Danish cancer registry, 2004–2009, Clin. Epidemiol. 4 (Suppl. 2) (2012) 17–23.
[10] N. Eisemann, A. Waldmann, A. Katalinic, Imputation of missing values of tumour stage in population-based cancer registration, BMC Med. Res. Methodol. 11 (2011) 129.
[11] A. Marshall, D.G. Altman, P. Royston, R.L. Holder, Comparison of techniques for handling missing covariate data within prognostic modelling studies: a simulation study, BMC Med. Res. Methodol. 10 (2010) 7.
[12] M.T. Redaniel, A. Laudico, M.R. Mirasol-Lumague, A. Gondos, G. Uy, H. Brenner, Inter-country and ethnic variation in colorectal cancer survival: comparisons between a Philippine population, Filipino-Americans and Caucasians, BMC Cancer 10 (2010) 100.
[13] Q. Luo, S. Egger, X.Q. Yu, D.P. Smith, D.L. O'Connell, Validity of using multiple imputation for "unknown" stage at diagnosis in population-based cancer registry data, PLoS One 12 (6) (2017) e0180033.
[14] J.A. Sterne, I.R. White, J.B. Carlin, et al., Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls, BMJ 338 (2009) b2393.
[15] World Health Organisation, ICD-10 International Statistical Classification of Disease and Related Health Problems, Available at: (2016) (Accessed 16 February 2018), http://apps.who.int/classifications/icd10/browse/2016/en.
[16] J.N. Armitage, J.H. van der Meulen, Identifying co-morbidity in surgical patients using administrative data with the Royal College of Surgeons Charlson Score, Br. J. Surg. 97 (5) (2010) 772–781.
[17] National Prostate Cancer Audit, Third Year Annual Report - Results of the NPCA Prospective Audit and Patient Survey, Available at: (2016) (Accessed 16 February 2018), http://www.npca.org.uk/annual-report-2016/.
[18] I.R. White, P. Royston, A.M. Wood, Multiple imputation using chained equations: issues and guidance for practice, Stat. Med. 30 (4) (2011) 377–399.
[19] J. Gurney, D. Sarfati, J. Stanley, et al., Unstaged cancer in a population-based registry: prevalence, predictors and patient prognosis, Cancer Epidemiol. 37 (4) (2013) 498–504.
[20] A.C. Klassen, F. Curriero, M. Kulldorff, A.J. Alberg, E.A. Platz, S.T. Neloms, Missing stage and grade in Maryland prostate cancer surveillance data, 1992–1997, Am. J. Prev. Med. 30 (2 Suppl) (2006) S77–87.
[21] R.M. Merrill, A. Sloan, A.E. Anderson, K. Ryker, Unstaged cancer in the United States: a population-based study, BMC Cancer 11 (2011) 402.
[22] S.P. Elliott, D.P. Johnson, S.L. Jarosek, B.R. Konety, O.O. Adejoro, B.A. Virnig, Bias due to missing SEER data in D'Amico risk stratification of prostate cancer, J. Urol. 187 (6) (2012) 2026–2031.
[23] M. Radespiel-Troger, K. Geiss, A. Gartig-Daugs, M. Meyer, Registration completeness and tumour-node-metastases category distribution in prostatic and testicular cancer in Bavaria, Eur. J. Cancer Prev. 17 (3) (2008) 230–237.
[24] K. Tomic, M. Westerberg, D. Robinson, H. Garmo, P. Stattin, Proportion and characteristics of men with unknown risk category in the National Prostate Cancer register of Sweden, Acta Oncol. 55 (12) (2016) 1461–1466.
[25] L. Barlow, K. Westergren, L. Holmberg, M. Talback, The completeness of the Swedish Cancer register: a sample survey for year 1998, Acta Oncol. 48 (1) (2009) 27–33.
[26] C.J. Bradley, J.P. Clement, C. Lin, Absence of cancer diagnosis and treatment in elderly Medicaid-insured nursing home residents, J. Natl. Cancer Inst. 100 (1) (2008) 21–31.
[27] S.M. Koroukian, F. Xu, H. Beaird, M. Diaz, P. Murray, J.H. Rose, Complexity of care needs and unstaged cancer in elders: a population-based study, Cancer Detect. Prev. 31 (3) (2007) 199–206.
[28] J.L. Worthington, S.M. Koroukian, G.S. Cooper, Examining the characteristics of unstaged colon and rectal cancer cases, Cancer Detect. Prev. 32 (3) (2008) 251–258.
[29] A.V. D'Amico, R. Whittington, S.B. Malkowicz, et al., Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer, JAMA 280 (11) (1998) 969–974.

4 SKELETAL-RELATED EVENTS

4.1 Research Paper 2

Title: Identifying skeletal-related events for prostate cancer patients in routinely collected hospital data.

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Student ID Number	LSH1800100	**Title**	Dr
First Name(s)	Matthew		
Surname/Family Name	Parry		
Thesis Title	Use of routinely collected hospital data to explore access to and outcomes from different radiotherapy treatment strategies for locally advanced prostate cancer: national population-based studies.		
Primary Supervisor	Professor Jan van der Meulen		

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SECTION E

Student Signature	M. Parry
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Identifying skeletal-related events for prostate cancer patients in routinely collected hospital data

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ABSTRACT

Background: Non-osteoporotic skeletal-related events (SREs) are clinically important markers of disease progression in prostate cancer. We developed and validated an approach to identify SREs in men with prostate cancer using routinely-collected data.

Methods: Patients diagnosed with prostate cancer between January 2010 and December 2013 were identified in the National Prostate Cancer Audit, based on English cancer registry data. A coding framework was developed based on diagnostic and procedure codes in linked national administrative hospital and routinely-collected radiotherapy data to identify SREs occurring before December 2015. Two coding definitions of SREs were assessed based on whether the SRE codes were paired with a bone metastasis code (*'specific definition'*) or used in isolation (*'sensitive definition'*). We explored the validity of both definitions by comparing the cumulative incidence of SREs from time of diagnosis according to prostate cancer stage at diagnosis with death as a competing risk.

Results: We identified 40,063, 25,234 and 13,968 patients diagnosed with localised, locally advanced and metastatic disease, respectively. Using the specific definition, we found that the 5-year cumulative incidence of SREs was 1.0 % in patients with localised disease, 6.0 % in patients with locally advanced disease, and 42.3 % in patients with metastatic disease. Using the sensitive definition, the corresponding cumulative incidence figures were 9.0 %, 14.9 %, and 44.4 %, respectively.

Conclusion: The comparison of the cumulative incidence of SREs identified in routinely collected hospital data, based on a specific coding definition in patients diagnosed with different prostate cancer stage, supports their validity as a clinically important marker of cancer progression.

1. Introduction

Prognostic or therapeutic determinants of the outcomes of prostate cancer patients often need a long follow-up period due to the natural history of this disease, which may be protracted. In order to report on patient survival a long follow-up is required. Markers of disease progression – or disease recurrence after initial successful treatment – could therefore be attractive alternative outcomes because they occur

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earlier in the course of the disease [1].

National or regional cancer registries are highly effective at identifying patients who have been diagnosed with cancer but they often fail to recognise patients whose cancer has progressed or recurred. This is also true of many cancer trials, where long-term follow up is often restricted, resulting in a failure to detect events that occur late in the course of the disease. Administrative hospital data in the United States and Denmark have been used to identify one of the key progression markers in prostate cancer, non-osteoporotic skeletal-related events (SREs) [2–7]. These encompass pathological fractures, spinal cord compression, radiotherapy for bone metastases, or bone surgery. This highlights the possibility of using this measured event as a marker of disease progression or recurrence, allowing for an observation of the true natural history of prostate cancer, and as a clinically important event in its own right.

We developed a coding framework in data available in the National Prostate Cancer Audit to identify non-osteoporotic SREs in routinely collected hospital data, consisting of three national datasets linked at patient level. We validated this framework firstly by assessing how often identified SREs were 'paired' with a diagnosis code for bone metastasis, secondly by estimating the 5-year cumulative incidence of SREs according to prostate cancer stage at the time of diagnosis, and thirdly by comparing the incidence of SREs observed with our coding framework against results of other studies.

2. Material and methods

2.1. Patient population

We identified 152,851 men diagnosed with prostate cancer between January 1, 2010 and December 31, 2013 in the National Prostate Cancer Audit [8], according to the International Classification of Diseases, 10th Edition (ICD-10) code for prostate cancer (C61) [9] available in English cancer registry data. Men were categorised according to their cancer stage at the time of diagnosis (localised, locally advanced, or metastatic prostate cancer), according to a method developed by the National Prostate Cancer Audit [10]. This categorisation is based on criteria recommended by the UK National Institute for Health and Care Excellence [11]. It uses Gleason score and TNM stage items that are available in the English cancer registry. Patients with M1 were categorised as having metastatic disease and in the remaining patients anyone with N1, T stage ≥ 3, Gleason score ≥ 8 or PSA > 20 were categorised as having locally advanced disease. The cancer registry also provided the date of diagnosis.

The cancer registry dataset was linked to the Hospital Episode Statistics (HES) database [12], an administrative database of all hospital episodes in the English NHS (also including mortality data from the Office for National Statistics) and to the National Radiotherapy Dataset (RTDS) [13], a database of all radiotherapy treatment episodes in England. Follow-up was available up to December 31, 2015. Diagnosis codes in HES are based on ICD-10 codes and procedure codes according to the fourth revision of the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS-4) [14]. Men with missing data for cancer stage at the time of diagnosis (n = 63,586) were excluded (Fig. 1).

2.2. Coding philosophy

Men who develop metastatic disease cannot reliably be identified as such in the English cancer registry or HES database because they are not always admitted to hospital and if admitted, the presence of metastatic disease is not always recorded. For that reason, we aimed to identify the first occurrence of a SRE, given that it is a serious complication of metastatic prostate cancer that typically results in a hospital-related treatment episode. The cumulative incidence of SREs underestimates the overall rate of disease progression, but it is likely to be a reliable and robust reflection of a clinically important, serious and costly complication of metastatic disease.

Our coding framework detects non-osteoporotic SREs in three ways. First, we identified diagnosis codes in HES for 'pathological fractures' or 'spinal cord compression'. Second, we identified procedure codes in HES for 'bone surgery'. Third, we identified codes in the linked RTDS to identify palliative radiotherapy.

2.3. Diagnosis codes

Based on earlier studies, a comprehensive a priori list of diagnosis codes related to SREs was generated. This list was informed by previous publications [15] and expert input from the co-authors who had a range of clinical backgrounds (MGP, AS, PC, HP, NC, AA). This step is termed *'forward coding'*. Codes for osteoporosis with pathological fractures (M800-9) were not included within this forward coding step in order to include only pathological fractures caused by bone metastases and not those solely caused by osteoporosis (given that men with prostate cancer are at risk of both). This is particularly relevant in light of the recent findings of the ERA-223 trial which set out to investigate the combination effect of adding radium-223 to abiraterone acetate and prednisolone/prednisolone in patients with castration-resistant metastatic prostate cancer. Radium-223 was shown to be contributing to an increased risk of osteoporotic fractures and led to the exclusion of osteoporotic events in this study [16].

The records of the hospital episodes in the HES database, identified through forward coding, were explored for additional common diagnosis codes that are likely to be related to a SRE. Diagnosis codes found through this step of *'backward coding'* were added to the code list. Backward coding was used because it is likely to add codes that are able to capture the idiosyncrasies of real-world coding practice that are difficult to identify otherwise. Expert input from the co-authors was again used to ensure that inclusion of these additional codes was appropriate.

2.4. Procedure codes

In an earlier study [14] forward coding, was used to identify procedure codes related to surgery for bone metastases in the HES data set. Backward coding was also used to search for additional procedure codes.

2.5. Radiotherapy codes

Linkage to the RTDS was used to identify patients who had undergone radiotherapy for prostate cancer. Men were considered to have undergone radiotherapy to metastatic sites if in linked RTDS records the treatment region was coded as 'metastasis', if the treatment intent was coded as 'non-curative' and treatment region was missing, or if a radiotherapy episode occurred after a hospital episode in the HES database that included a diagnosis code for bone metastasis ('secondary malignant neoplasm of bone and marrow' [C795]). We only used a single code for bone metastasis (C795) for this purpose because other possible diagnosis codes for bone metastases ('malignant neoplasm of vertebral column' (C412) or 'malignant neoplasm of pelvic bones, sacrum and coccyx' (C414)) were never observed.

2.6. Validation

We validated the coding framework in three steps. First, we looked at how often diagnosis and procedure codes related to a SRE were 'paired' with the diagnosis code for bone metastasis (C795) in the same hospital episode in the HES database. In the cases where the SRE was identified in the RTDS, pairing was defined as the occurrence of a diagnosis code for bone metastasis in a hospital episode which was within 6 months of the palliative radiotherapy start date as recorded in the

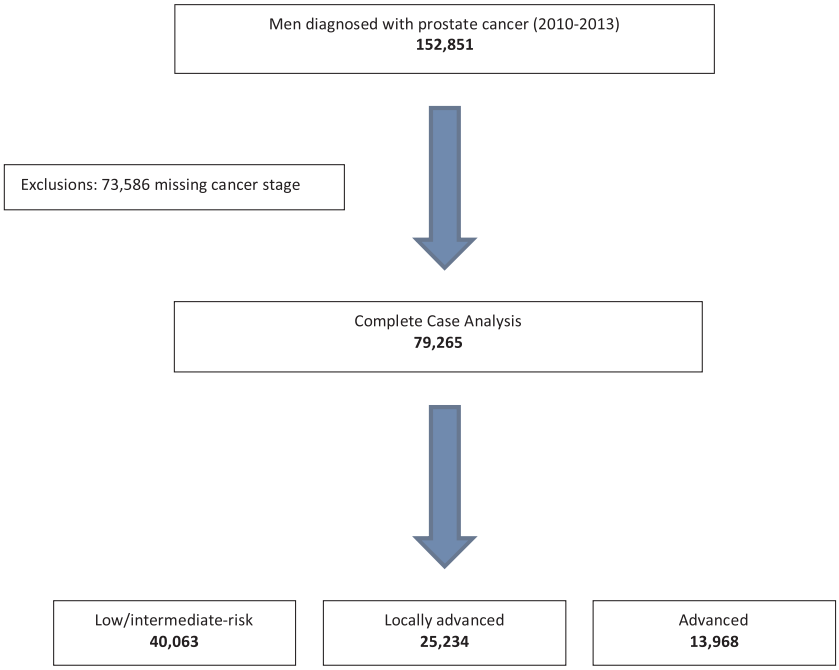

Fig. 1. Flow chart of men included in the study.

RTDS. This step reflects that we can distinguish two coding definitions: a 'specific definition' in which the SRE codes are paired with a code for bone metastasis, and a 'sensitive definition' in which SRE codes are used in isolation.

Second, we investigated the association of the cumulative incidence of SREs after prostate cancer diagnosis with cancer stage at the time of diagnosis. Third, we compared the incidence of SREs, observed with our coding framework, with the results of other studies.

2.7. Statistical analysis

The 5-year cumulative incidence of SREs was estimated, with death being treated as a competing event [17]. Men were followed up from the date of their prostate cancer diagnosis until their first SRE or until December 31, 2015, whichever came first. The data analysis was undertaken using Stata version 15 (StataCorp LLC, College Station, TX, USA).

3. Results

3.1. Coding framework to identify SREs in administrative hospital data and routinely-collected radiotherapy data

We included 79,265 men of whom 40,063 had localised disease, 25,234 had locally advanced disease, and 13,968 had metastatic disease at the time of diagnosis. The cohort was followed up and SREs were identified based on the coding framework generated through forward coding. Using the records of patients identified as having a SRE in this way, we identified two further diagnosis codes through backward coding: 'fracture of bone in neoplastic disease' (M907) and 'myelopathy in disease classified elsewhere' (G992). The final list for SRE codes included in the coding framework is summarised in Table 1.

Table 1
ICD-10 diagnosis code and OPCS-4 procedure code definitions for skeletal-related events.

	Code Definition
ICD-10 diagnosis codes	
Pathological fracture	
M485	Collapsed vertebra, not elsewhere classified
M495	Collapsed vertebra in diseases classified elsewhere
M844	Pathological fracture, not elsewhere classified
M907*	Fracture of bone in neoplastic disease
Spinal cord compression	
G550	Nerve root and plexus compressions in neoplastic disease
G834	Cauda equine syndrome
G952	Other and unspecified spinal cord compression
G958	Unspecified disease of spinal cord
G959	Other specified disease of spinal cord
G992*	Myelopathy in diseases classified elsewhere
OPCS-4 procedure codes	
Spinal surgery	
V22-7, V67-8	Decompression operations on spine
V28	Insertion of lumbar interspinous process spacer
V38-4	Fusion of joint/stabilisation of spine
V41	Instrumental correction of deformity of spine
V43, V47	Extirpation of lesion/biopsy of spine
V44-6,	Decompression/reduction/fixation of fracture of spine
V55	Levels of spine
Bone surgery	
W05	Prosthetic replacement of bone
W08-9	Excision of bone/extirpation of lesion of bone
W16	Division of bone
W19-26	Reduction of fracture
W28, W30	Internal/external fixation of bone
W37-41, W93-5	Replacement of hip/knee joint
W46-8	Prosthetic replacement of head of femur
W65-7	Reduction of traumatic dislocation of joint

* Codes identified through 'backward coding'. See Material and Methods for further explanation.

3.2. Validation

Table 2 shows how frequently the SRE-related diagnosis codes were paired with a bone metastasis code (C795), according to prostate cancer stage at diagnosis. These frequencies were high for patients with metastatic disease (all above 80 %). They were lower for patients with localised or locally advanced disease, especially for the diagnosis codes with less specific definitions, including 'collapsed vertebra, not elsewhere classified' (M485), 'unspecified disease of spinal cord' (C958),

Table 2
Frequency of the first occurrence of codes for skeletal-related events with and without a diagnosis code for bone metastasis, stratified by prostate cancer stage at diagnosis.

First occurrence of a SRE* code per man	Prostate cancer stage at diagnosis					
	Metastatic		Locally advanced		Localised	
	SRE paired with bone metastasis n (%)	SRE not paired with bone metastasis n (%)	SRE paired with bone metastasis n (%)	SRE not paired with bone metastasis n (%)	SRE paired with bone metastasis n (%)	SRE not paired with bone metastasis n (%)
DIAGNOSIS CODES						
Pathological fracture codes						
Any code (n = 1313)	918 (95.8)	40 (4.2)	146 (62.4)	88 (37.6)	51 (42.2)	70 (57.9)
M485 (n = 206)	62 (80.5)	15 (19.5)	13 (17.8)	60 (82.2)	7 (12.5)	49 (87.5)
M495 (n = 294)	233 (99.6)	1 (0.4)	32 (88.9)	4 (11.1)	21 (87.5)	3 (12.5)
M844 (n = 127)	57 (82.6)	12 (17.4)	9 (29.0)	22 (71.0)	7 (25.9)	20 (74.1)
M907 (n = 794)	635 (97.2)	18 (2.8)	101 (91.8)	9 (8.2)	26 (83.9)	5 (16.1)
Spinal cord compression codes						
Any code (n = 1848)	1409 (97.4)	37 (2.6)	181 (69.6)	79 (30.4)	55 (38.7)	87 (61.3)
G550 (n = 441)	378 (99.0)	4 (1.1)	45 (97.7)	2 (4.3)	12 (100)	0 (0)
G834 (n = 207)	161 (98.2)	3 (1.8)	26 (84.9)	5 (16.1)	5 (41.7)	7 (58.3)
G952 (n = 661)	505 (93.5)	35 (6.5)	62 (74.8)	22 (26.2)	20 (54.1)	17 (46.0)
G958 (n = 32)	11 (84.6)	2 (15.4)	3 (16.7)	15 (83.3)	1 (9.1)	10 (90.9)
G959 (n = 50)	21 (87.5)	3 (12.5)	3 (42.9)	42 (31.1)	0 (0)	8 (100)
G992 (n = 983)	748 (97.7)	18 (2.4)	93 (68.9)	4 (4.1)	28 (34.2)	54 (65.9)
PROCEDURE CODES						
Surgery codes						
OPCS-4 V/W codes (n = 5186)**	872 (75.4)	284 (24.6)	128 (7.4)	1603 (92.6)	43 (1.9)	2256 (98.1)
RTDS palliative radiotherapy codes*						
RT episodes with valid HES record**** (n = 5115)	3795 (89.7)	438 (10.4)	585 (77.1)	174 (22.9)	89(72.4)	34 (27.6)

* Skeletal-related event; ** See Table 2; *** Radiotherapy Dataset; **** Only men with a HES record within 6 months of the start date of radiotherapy.

'other specified disease of spinal cord' (C959), and 'myelopathy in diseases classified elsewhere' (C992).

The surgical procedure codes were also frequently paired with a code for bone metastasis in men with metastatic disease at diagnosis (on average 75.4 %). This frequency was again considerably lower in men with localised or locally advanced disease, which can be explained by the broad definitions of the included procedure codes for bone surgery.

The linked RTDS records indicating radiotherapy for metastasis were paired with a bone metastasis code in 78.4% of men with metastatic disease at diagnosis. Lower frequencies were again observed in men with localised or locally advanced disease.

These results demonstrate that a sensitive coding definition of SREs (SRE codes used without the requirement for pairing with a bone metastasis code) can lead to a substantial overestimation of the occurrence of skeletal events, especially in men diagnosed with localised or locally advanced disease. For example, we found that the 5-year cumulative incidence of SREs for men diagnosed with metastatic disease was very similar, irrespective of whether the sensitive definition (44.4 %) or the specific definition (42.3 %) was used (Table 3 and Fig. 2). However, the difference in the cumulative incidence of SREs according to whether a sensitive or specific definition was used was much larger for men with localised disease (9.0 % and 1.0 %, respectively) and locally advanced disease (14.9 % and 6.0 %, respectively).

3.3. Further exploration of the diagnosis and procedure codes related to SRE

According to the specific coding definition of SREs, where SRE codes required pairing with a bone metastasis code, the majority of men who experienced a pathological fracture, spinal cord compression or both had some form of surgical and/or radiation-based intervention (77.1 %, 86.0 % and 93.7 %, respectively; Table 4). In men diagnosed with metastatic prostate cancer, the most common SRE was radiotherapy for bone metastases with a 5-year cumulative incidence of 38.5 %. The corresponding figures for pathological fractures, spinal cord compression and bone surgery were 6.7 %, 10.4 % and 6.5 %, respectively.

Table 3
Cumulative incidence of skeletal-related events according to prostate cancer stage at diagnosis for men with prostate cancer.

Cancer stage at diagnosis	5-year cumulative incidence (%)	95% CI		
Specific definition				
Localised	1.0	0.8	–	1.2
Locally advanced	6.0	5.6	–	6.5
Metastatic	42.3	41.3	–	43.3
Sensitive definition				
Localised	9.0	8.6	–	9.5
Locally advanced	14.9	14.3	–	15.6
Metastatic	44.4	43.4	–	45.5

4. Discussion

4.1. Overview

A coding framework was developed to identify non-osteoporotic SREs in men diagnosed with prostate cancer based on diagnosis codes (for pathological fractures and spinal cord compression) and procedure codes (for bone surgery) in administrative hospital data, and palliative radiotherapy codes in a routinely collected radiotherapy dataset.

We demonstrated that a specific coding definition for a SRE (requiring a paired diagnosis code for bone metastasis) produced a very similar 5-year cumulative SRE incidence in men with metastatic disease, at the time of their prostate cancer diagnosis, as a sensitive coding

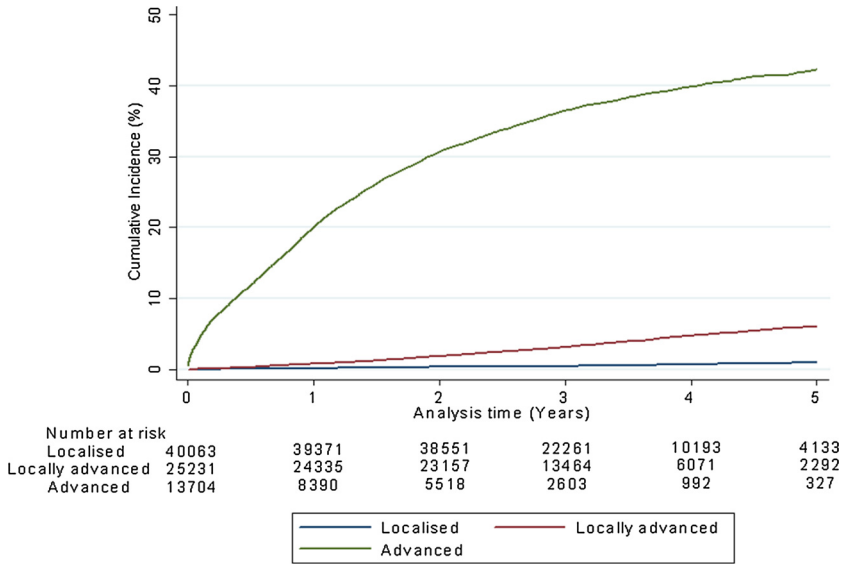

Fig. 2. Cumulative incidence of the first occurrence of a skeletal-related event in men with prostate cancer, according to the specific definition, stratified by cancer stage at diagnosis.

Table 4
Frequency that patients with pathological fractures and/or spinal cord compression, according to the specific definition, undergo bone surgery and/or palliative radiotherapy.

	Procedural skeletal-related event				
Diagnostic skeletal-related event	Bone surgery n (%)	Radiotherapy n (%)	Both n (%)	Neither n (%)	Total n (%)
Pathological fracture	120	247	189	198	754
	(15.9)	(32.8)	(25.1)	(26.3)	(100)
Spinal cord compression	37	924	131	192	1284
	(2.9)	(72.0)	(10.2)	(15.0)	(100)
Both	26	195	119	21	361
	(7.2)	(54.0)	(33.0)	(5.8)	(100)
Neither	225	3888	196	72,557	76,866
	(0.3)	(5.1)	(0.3)	(94.4)	(100)
Total	408	5,254	635	72,968	79,265
	(0.5)	(6.6)	(0.8)	(92.1)	(100)

definition (not requiring a paired diagnosis code for bone metastasis). However, the 5-year cumulative incidences were much lower for patients with localised or locally advanced disease at diagnosis when the specific coding definition was used as opposed to the sensitive coding definition. These results suggest that the true-positive detection rates of SREs with specific and sensitive coding definitions are almost the same but that the false-positive detection rate with the specific coding definition is much lower than that of the sensitive coding definition.

4.2. Comparison with other studies

Comparing the incidence of SREs observed with our coding framework against results of other studies is the third step of the validation process. Our study is the largest study to report on the incidence of SREs in prostate cancer and is the first to do so in the UK using national population-based data for almost 80,000 patients with prostate cancer. We found that 39% of men with metastatic prostate cancer at the time of diagnosis experienced at least one SRE within 5 years. Six observational studies have used large administrative datasets to report on SREs in metastatic prostate cancer [2–7]. Five of these studies have been conducted in the US [2–4,6,7] and four of these five used linked SEER-Medicare data [2–4,6]. The most recent of these studies was published in 2016 and used ICD-9 diagnosis codes and Healthcare Common Procedure Coding System (HCPCS) procedure codes to identify SREs in 3297 men diagnosed with metastatic disease between 2004 and 2009 [2]. The coding framework used in this study compared well to the one used in ours but the authors could not specify the target of radiotherapy. 40% of the men in this study experienced at least one SRE during a median follow-up of 19 months.

Similar results, also based on linked SEER-Medicare data, were shown for a cohort of 4404 men diagnosed with metastatic prostate cancer between 2005 and 2009 (44 % experienced SREs after a median follow-up of 16.6 months) [3] and for a similar cohort of 9746 men diagnosed between 1999 and 2005, 44 % experienced SREs after a median follow-up of 26 months) [4].

The fourth study that used SEER-Medicare data explored the impact of varying definitions of SREs in 8997 patients diagnosed between 2000 and 2009 [6]. This study demonstrated that the observed SRE incidence depended on the codes included in the coding framework (specific versus sensitive codes), with codes used to identify pathological fractures being the most affected by differing definitions of a SRE. SRE incidence ranged from 46 % ('base case' SRE definition) to 43 % ('alternative' SRE definition) after a median follow-up of 18 months. The base case and alternative definitions differed with respect to the use of combinations of more sensitive and more specific definitions for the various SRE-related diagnoses and procedures.

The fifth US study included 3919 men diagnosed with bone metastases between 2002 and 2011 and recorded in the Thomson MedStat MarketScan Commercial Claims and Encounters database. A higher SRE rate was reported at 53 % after a median follow-up of 16.1 months [7].

Finally, a Danish study analysed 3261 men diagnosed with bone metastases between 1999 and 2007 and reported similarly high SRE rates (cumulative incidence of 46.1 % at 1 year and 53.8 % at 5 years) [5].

We found a lower incidence of SREs than the six studies described above. An important explanation for this difference is that significant transitions have been made in the management of metastatic disease and that all patients included in our study were diagnosed in 2010 or later. New chemotherapeutic options have been shown to reduce the incidence of SREs and were not being used at the time of these older studies [18–22].

4.3. Methodological considerations

A major limitation of our work – and of all other studies in this area – is that we were reliant on the accuracy of the clinical coding in the routinely collected hospital data. However, the accuracy of these data has been shown to be high when compared to clinical notes and is sufficiently robust to support its use in research [23].

Incomplete information on cancer stage at the time of diagnosis is a further limitation because men with missing stage were excluded. We have previously shown that stage data is more often missing in prostate cancer patients older than 80 years and in those from a more socio-economically deprived background [24]. However, it is unlikely that this selective inclusion will have had a major impact on our results (comparing SRE incidence according to cancer stage at diagnosis), because there is no obvious plausible mechanism that would explain why cancer stage at diagnosis would have a different impact on the occurrence of SREs according to whether or not this information had been recorded.

Lastly, the use of administrative hospital data ensures that only severe events that require hospital events are captured. In this way, asymptomatic vertebral fractures are not identified with our coding framework which limits any potential over-estimation of the SRE incidence.

A key strength of our study is that the administrative hospital data and the routinely collected radiotherapy data are likely to have identified the majority of the relevant hospital and radiotherapy episodes. This is because more than 95 % of patients diagnosed with prostate cancer in England are treated in the NHS, making it a nationally representative patient cohort. Furthermore, it is extremely rare that patients who have had their initial treatment in the English NHS will switch to a private healthcare provider later in their treatment pathway and this minimises underestimation of the SRE incidence due to loss to follow-up [25].

A unique feature of our study is that we compared the cumulative incidence of SREs according to prostate cancer stage at the time of diagnosis. This comparison allowed us to compare the performance of specific and sensitive coding definitions allowing for an assessment of coding consistency. The preference to use the specific coding definition of SREs, where SRE codes require pairing with a bone metastasis code, prevents substantial misclassification and overestimation of SREs and adds to the reliability of the coding framework.

Lastly, by using backward coding we created greater certainty that our coding framework also included diagnosis and procedure codes that are difficult to determine a priori. Two frequently occurring diagnosis codes were added to our coding framework which will have further reduced the extent to which our approach underestimates the SRE incidence.

4.4. Implications

It is the first time that an administrative hospital database using ICD-10 diagnosis codes has been used to detect patients with a SRE. Given our explicit and transparent coding framework, our results are reproducible and applicable to other national administrative databases that use the same diagnosis codes and related procedure codes. Equally a similar coding framework could be applied to other cancer groups. Based on these results, we recommend that the specific coding definition for a SRE (requiring a paired diagnosis code for bone metastasis) is used in large-scale studies of routinely collected data to identify disease progression and compare treatment outcomes in prostate cancer.

In many countries, cancer registries are highly accurate and complete in identifying patients diagnosed with cancer, but their performance is considerably poorer in identifying disease progression. We have shown, along with studies from outside the UK, that administrative hospital data can be used to this end. The coding framework outlined in this paper can be used to detect SREs as a key outcome for comparisons of prostate cancer treatments. Capturing events other than death is important in order to measure highly relevant clinical outcomes which happen earlier so that a shorter follow-up is required for studies of therapeutic outcomes in prostate cancer patients.

The treatment options for metastatic prostate cancer are rapidly developing and now chemotherapy, in the neoadjuvant and castrate-resistant settings, is able to reduce the incidence of SREs and prolong survival [26]. The ability to identify the occurrence of SREs in a 'real-world' national population is paramount in order to describe disease trends and assess the impact of novel treatments and their value [27].

5. Conclusions

Combinations of diagnosis and procedure codes in administrative hospital data linked to a national radiotherapy dataset can be used to identify non-osteoporotic SREs across cancer stages. Identifying SREs based on these codes provides an accurate measure of cancer progression which can be used for comparing treatment outcomes in routinely collected hospital data according to prognostic or therapeutic determinants.

Declaration of Competing Interest

J.v.d.M. reports a contract with the Healthcare Quality Improvement Partnership (HQIP) (www.hqip.org.uk) for the provision of the National Prostate Cancer Audit (www.npca.org,uk).

H.P. has attended and received honoraria for advisory boards, travel expenses to medical meetings, and served as a consultant for AstraZeneca, Astellas, Janssen, Sanofi Aventis, Takeda, Ipsen, Ferring, Sandoz, and Novartis.

N.W.C. has attended and received honoraria for advisory boards, travel expenses to medical meetings, and served as a consultant for AstraZeneca, Astellas, Bayer, Janssen, Sanofi Aventis, Ipsen and Ferring.

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Author contribution

Designed the work: M.G.P., T.E.C., J.v.d.M., A.A.

Analysed and interpreted data: M.G.P., T.E.C., N.W.C., H.P., J.v.d.M., A.A.

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References

[1] W. Xie, M.M. Regan, M. Buyse, S. Halabi, P.W. Kantoff, O. Sartor, et al., Metastasis-free survival is a strong surrogate of overall survival in localized prostate Cancer, J. Clin. Oncol. 35 (27) (2017) 3097–3104.
[2] J.A. McDougall, A. Bansal, B.H. Goulart, J.S. McCune, A. Karnopp, C. Fedorenko, et al., The clinical and economic impacts of skeletal-related events among medicare enrollees with prostate cancer metastatic to bone, Oncologist. 21 (3) (2016) 320–326.
[3] A. Hussain, A. Aly, C. Daniel Mullins, Y. Qian, J. Arellano, E. Onukwugha, Risk of skeletal related events among elderly prostate cancer patients by site of metastasis at diagnosis, Cancer Med. 5 (11) (2016) 3300–3309.
[4] N. Sathiakumar, E. Delzell, M.A. Morrisey, C. Falkson, M. Yong, V. Chia, et al., Mortality following bone metastasis and skeletal-related events among men with prostate cancer: a population-based analysis of US Medicare beneficiaries, 1999-2006, Prostate Cancer Prostatic Dis. 14 (2) (2011) 177–183.
[5] M. Norgaard, A.O. Jensen, J.B. Jacobsen, K. Cetin, J.P. Fryzek, H.T. Sorensen, Skeletal related events, bone metastasis and survival of prostate cancer: a population based cohort study in Denmark (1999 to 2007), J Urol. 184 (1) (2010) 162–167.
[6] A. Aly, E. Onukwugha, C. Woods, C.D. Mullins, Y. Kwok, Y. Qian, et al., Measurement of skeletal related events in SEER-Medicare: a comparison of claims-based methods, BMC Med Res Methodol. 15 (2015) 65.
[7] M. Hagiwara, T.E. Delea, M.W. Saville, K. Chung, Healthcare utilization and costs associated with skeletal-related events in prostate cancer patients with bone metastases, Prostate Cancer Prostatic Dis. 16 (1) (2013) 23–27.
[8] National Prostate Cancer Audit, First Year Annual Report - Organisation of Services and Analysis of Existing Clinical Data, (2014) Available at: https://www.npca.org.uk/content/uploads/2014/11/NPCA-Annual-Report-FINAL-10_11_14.pdf (Accessed January 8, 2018).
[9] World Health Organisation. International Statistical Classification of Diseases and Related Health Problems (10th Revision). Available at: http://www.who.int/classifications/icd/ICD10Volume2_en_2010.pdf (Accessed September 28, 2017).
[10] National Prostate Cancer Audit, Third Year Annual Report - Results of the NPCA Prospective Audit and Patient Survey, (2016) Available at: http://www.npca.org.uk/annual-report-2016 / (Accessed 16 February 2018).
[11] National Institute for Health and Care Excellence, Prostate Cancer: Diagnosis and Management, Available at: http://www.nice.org.uk/guidance/CG175 (Accessed February 16, 2018). 2014.
[12] National Health Service. Hospital Episode Statistics Available at: http://www.hesonline.nhs.uk (accessed January 15, 2017).
[13] National Cancer Registration and Analysis Service. National Radiotherapy Dataset (RTDS) Available at: http://www.ncin.org.uk/collecting_and_using_data/rtds (Accessed December 11, 2017).
[14] NHS Digital. NHS Classifications Service: OPCS Classifications of Interventions and Procedures Version 4.4; Available at: http://systems.digital.nhs.uk/data/clinicalcoding/codingstandards/opcs4 (Accessed 28 September, 2017).
[15] K.J. Kowalczyk, X. Gu, P.L. Nguyen, S.R. Lipsitz, Q.D. Trinh, J.H. Lynch, et al., Optimal timing of early versus delayed adjuvant radiotherapy following radical prostatectomy for locally advanced prostate cancer, Urol Oncol. 32 (3) (2014) 303–308.
[16] M. Smith, C. Parker, F. Saad, K. Miller, B. Tombal, Q.S. Ng, et al., Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial, Lancet Oncol. 20 (3) (2019) 408–419.
[17] V.B.M. Coviello, Cumulative incidence estimation in the presence of competing risks, Stata J. 4 (2004) 103–112.
[18] G. Gravis, J.M. Boher, F. Joly, M. Soulie, L. Albiges, F. Priou, et al., Androgen deprivation therapy (ADT) plus docetaxel versus ADT alone in metastatic non castrate prostate Cancer: impact of metastatic burden and long-term survival analysis of the randomized phase 3 GETUG-AFU15 trial, Eur Urol. 70 (2) (2016) 256–262.
[19] G. Gravis, K. Fizazi, F. Joly, S. Oudard, F. Priou, B. Esterni, et al., Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial, Lancet Oncol. 14 (2) (2013) 149–158.
[20] N.D. James, M.R. Sydes, N.W. Clarke, M.D. Mason, D.P. Dearnaley, M.R. Spears, et al., Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial, Lancet. 387 (10024) (2016) 1163–1177.
[21] C.J. Sweeney, Y.H. Chen, M. Carducci, G. Liu, D.F. Jarrard, M. Eisenberger, et al., Chemohormonal therapy in metastatic hormone-sensitive prostate Cancer, N. Engl J Med. 373 (8) (2015) 737–746.
[22] M.E. Taplin, B. Montgomery, C.J. Logothetis, G.J. Bubley, J.P. Richie, B.L. Dalkin, et al., Intense androgen-deprivation therapy with abiraterone acetate plus leuprolide acetate in patients with localized high-risk prostate cancer: results of a randomized phase II neoadjuvant study, J Clin Oncol. 32 (33) (2014) 3705–3715.
[23] E.M. Burns, E. Rigby, R. Mamidanna, A. Bottle, P. Aylin, P. Ziprin, et al., Systematic review of discharge coding accuracy, J. Public Health Oxf. (Oxf). 34 (1) (2012) 138–148.
[24] M.G. Parry, A. Sujenthiran, T.E. Cowling, S. Charman, J. Nossiter, A. Aggarwal, et al., Imputation of missing prostate cancer stage in English cancer registry data based on clinical assumptions, Cancer Epidemiol. 58 (2019) 44–51.
[25] A. Aggarwal, D. Lewis, A. Sujenthiran, S.C. Charman, R. Sullivan, H. Payne, et al., Hospital quality factors influencing the mobility of patients for radical prostate Cancer radiation therapy: a national population-based study, Int J Radiat Oncol Biol Phys. 99 (5) (2017) 1261–1270.
[26] L. Dong, R.C. Zieren, W. Xue, T.M. de Reijke, K.J. Pienta, Metastatic prostate cancer remains incurable, why? Asian J Urol. 6 (1) (2019) 26–41.
[27] Y. Lievens, R. Audisio, I. Banks, L. Collette, C. Grau, K. Oliver, et al., Towards an evidence-informed value scale for surgical and radiation oncology: a multi-stakeholder perspective, Lancet Oncol. 20 (2) (2019) e112–e123.

5 CENTRALISATION

5.1 Research Paper 3

Title: Impact of cancer service centralisation on the radical treatment of men with high-risk and locally advanced prostate cancer: a national cross-sectional analysis in England.

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Student ID Number	LSH1800100	**Title**	Dr
First Name(s)	Matthew		
Surname/Family Name	Parry		
Thesis Title	Use of routinely collected hospital data to explore access to and outcomes from different radiotherapy treatment strategies for locally advanced prostate cancer: national population-based studies.		
Primary Supervisor	Professor Jan van der Meulen		

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Date	8/1/21

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Impact of cancer service centralisation on the radical treatment of men with high-risk and locally advanced prostate cancer: A national cross-sectional analysis in England

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In many countries, specialist cancer services are centralised to improve outcomes. We explored how centralisation affects the radical treatment of high-risk and locally advanced prostate cancer in the English NHS. 79,085 patients diagnosed with high-risk and locally advanced prostate cancer in England (April 2014 to March 2016) were identified in the National Prostate Cancer Audit database. Poisson models were used to estimate risk ratios (RR) for undergoing radical treatment by whether men were diagnosed at a regional co-ordinating centre ('hub'), for having surgery by the presence of surgical services on-site, and for receiving high dose-rate brachytherapy (HDR-BT) in addition to external beam radiotherapy by its regional availability. Men were equally likely to receive radical treatment, irrespective of whether they were diagnosed in a hub (RR 0.99, 95% CI 0.91–1.08). Men were more likely to have surgery if they were diagnosed at a hospital with surgical services on site (RR 1.24, 1.10–1.40), and more likely to receive additional HDR-BT if they were diagnosed at a hospital with direct regional access to this service (RR 6.16, 2.94–12.92). Centralisation of specialist cancer services does not affect whether men receive radical treatment, but it does affect treatment modality. Centralisation may have a negative impact on access to specific treatment modalities.

Introduction

Approximately one third of all men with a new diagnosis of prostate cancer in England have locally advanced disease.[1] These men have a high risk of disease progression and cancer-related mortality, highlighting the importance of radical treatment in this group.[2,3] Contemporary data from the National Prostate Cancer Audit (NPCA) suggest that 27% of men with high-risk or locally advanced prostate cancer do not receive radical treatment with surgery or radiotherapy.[4] According to the NPCA[1] and the National Institute for Health and Care Excellence[5] risk stratification, high-risk localised disease is classified in the same group as 'locally advanced' disease.

There is a clear survival benefit for the combination of external beam radiation therapy (EBRT) and androgen deprivation

Key words: prostate cancer, under-treatment, centralisation, inequity, access
Additional Supporting Information may be found in the online version of this article.
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What's new?

More than one-quarter of men with high-risk or locally advanced prostate cancer in England do not receive radical treatment with radiotherapy or surgery, potentially owing to differences in treatment access. Here, prostate cancer service centralisation in England was investigated for potential impacts on treatment access. Among English patients in the National Prostate Cancer Audit database, centralisation had no impact on decisions to use radical treatment. It did, however, affect treatment option availability, with potential consequences for patient outcome. Patients were more likely to undergo surgery or high dose-rate brachytherapy when diagnosed at hospitals with direct links to these services.

therapy (ADT), over either treatment alone, and this combination is a standard of care for men with locally advanced prostate cancer.[6–8] Current UK National Institute for Health and Care Excellence (NICE) guidelines (2014) and European Association of Urology (EAU) guidelines (2017) also recommend combining high-dose rate brachytherapy (HDR-BT) with EBRT, for suitable men with high-risk prostate cancer.[5,9] Recently reported observational data are now beginning to favour combination therapy in terms of disease progression and mortality but utilisation of this treatment strategy has not been previously reported in England.[10]

Radical prostatectomy (RP) has historically been reserved for clinically localised disease but there is increasing evidence that it has a positive effect in high-risk men, and even in more advanced cases.[11] It is currently used in 22% of men with high-risk or locally advanced patients in England (2015/16).[4] Optimal use of RP as part of a multimodal approach is yet to be established but current guidelines advocate its use for selected patients.[12]

For over a decade, specialist radiotherapy and radical prostatectomy services for prostate cancer have been centralised in England, which has restricted the number of centres providing these specialist services and in turn increased the centres' average volume of procedures. The rationale for this centralisation is to optimise the quality of care men receive and to improve patient outcomes by focussing treatment in high-volume centres.[13,14] To co-ordinate access to these specialist services 48 specialist Multi-Disciplinary Teams (MDT) were set up across England. Each specialist MDT is made up of a regional referral network of hospitals within a specific geographical area of the country. Hospitals assigned as the lead of each regional referral network, or 'hub' site, act as regional co-ordinating centres. Each hub is usually a specialist centre for either radiotherapy, surgery or both and the other hospitals within the network act as 'spoke' hospitals. Most spoke hospitals are non-specialist centres and therefore have to refer to specialist centres for radical treatment, but a few provide one or more treatment modalities on-site.

The NPCA collected information regarding the organisation of prostate cancer services for each regional referral network and the specialist treatment services available on-site at each hospital.[15] Between April 2014 and March 2016, 138 hospitals in the English National Health Service (NHS) provided diagnostic facilities for prostate cancer, of which 53 were specialist surgical centres, 51 were specialist radiotherapy centres and 19 were specialist HDR-BT centres. Access to radiotherapy and surgical centres is available to every hospital within England *via* one of the 48 regional referral networks, however HDR-BT services are only available to hospitals within 24 of these regions, either directly or externally *via* a neighbouring regional referral network. HDR-BT has therefore become a super-specialised treatment modality within the complex, centralised system for prostate cancer care in England.

The hub-and-spoke model for prostate cancer care aims to improve outcomes while aiming to guarantee appropriate access, irrespective of the hospital where a patient is diagnosed. Despite this, studies have started to emerge highlighting that this centralisation process has led to an inequity of access to surgery in the treatment of other cancers, such as lung cancer and liver metastases in colorectal cancer.[15–17]

We therefore aim to assess whether cancer service centralisation impacts on the access to radical treatment, or on the specific type of radical treatment that men with high-risk and locally advanced prostate cancer receive in the English NHS.

Materials and Methods

Study population

The NPCA is a national clinical audit assessing the quality of services and care provided to men with prostate cancer in England and Wales. The NPCA has been reporting about the treatment and outcomes of all patients newly diagnosed with prostate cancer since April 2014.

All patients newly diagnosed with prostate cancer between April 1st 2014 and March 31st 2016 were identified in the NPCA database. This database includes relevant data items from the English Cancer Registry and data items specific to the NPCA, both supplied by Public Health England's National Cancer Registration and Analysis Service (NCRAS). Disease status was assigned according to a risk stratification algorithm previously described by the NPCA[1], and based on the NICE criteria[5], which uses NPCA data items for each cancer characteristic (Gleason score, PSA and TNM). TNM data used preferentially clinical cancer registry items and then pathological cancer registry items, in line with the Union for International Cancer Control (UICC) TNM 7th edition, taking staging information that was updated as much as possible by cancer registry staff. Gleason scores were based on prostate biopsy information. The patient cohort was restricted only to men with non-metastatic, high-risk or locally advanced disease

defined as any one of: Gleason score ≥ 8, PSA > 20 ng/mL or T3/T4 (±N1).

The NPCA database was linked at patient-level with two routine databases. Hospital Episode Statistics (HES) is a database of all hospital admissions in the English NHS and is a source of surgery-specific information about operation type and date.[18] The National Radiotherapy Data Set (RTDS) is a national database that contains standardised data from all NHS hospital providers of radiotherapy services in England.[19] 1495 men without a documented diagnosing hospital were excluded.

Baseline characteristics

English Cancer Registry data was used to identify the diagnosing hospital, the date of diagnosis, cancer characteristics, ethnicity and age at diagnosis for each man. Cancer characteristics were used for stratifying disease status but also to provide baseline information.

The Royal College of Surgeons (RCS) Charlson score was used to identify co-morbid conditions in the HES record based on co-morbidities that were recorded one year before a patient's prostate cancer diagnosis.[20] The Index of Multiple Deprivation (IMD) was used to categorise patients into five socioeconomic groups (1 = least deprived; 5 = most deprived) based on the areas in which they lived. The IMD ranks 32,482 areas, and each area covers a mean population of around 1500 people or 400 households. The five categories were fifths of the national IMD ranking of these areas.[21]

Outcome variables

The OPCS Classification of Interventions and Procedures (OPCS-4) code 'M61' was used to identify the men in the HES record who underwent an RP and the date of their operation.[22] The RTDS data item 'treatment modality' was used to select men who underwent EBRT and/or brachytherapy and the date of their treatment. Brachytherapy dosing information was used to identify the men who received HDR-BT.

Three binary outcome measures were used. The first was whether men with high-risk or locally advanced prostate cancer received any radical treatment (EBRT, brachytherapy, RP or a combination) within one year of diagnosis. The second was whether surgery was selected for the men who received radical treatment. The third was whether HDR-BT was provided for the men who received radiotherapy. Radical treatment was defined as the first treatment selected and therefore men receiving additional salvage treatment were included within the group according to their primary treatment.

Exposure variables

One key aim of the NPCA was to assess the configuration and availability of specialist prostate cancer services in England. In 2014, the NPCA undertook an organisational survey of all NHS hospitals across England. Questionnaires established the availability and location of core diagnostic, treatment and support services for the management of non-metastatic prostate cancer. The survey was updated in December 2016 to reflect changing service organisation.

This organisational survey was used to provide information about available services at each hospital with regards to RP, EBRT and HDR-BT, as well as other services. Binary variables were created to express the hub or spoke status of each diagnosing hospital, the provision of RP services on-site at each diagnosing hospital, and the availability of HDR-BT services in each regional referral network. These three variables were the main exposure variables for our study.

Statistical analysis

Multivariable multilevel Poisson regression, with robust standard errors, was used to estimate the risk ratio of receiving radical treatment by whether men were diagnosed at a hub or spoke hospital, adjusted for age, ethnicity, socioeconomic deprivation status, Charlson score, T-stage, N-stage, Gleason score and PSA value.[23] A random intercept was modelled for each hospital to adjust for clustering within hospitals.[24]

A second regression model was performed for a cohort of men who received radical treatment to estimate the likelihood of receiving RP according to whether surgery was available on-site at the diagnosing hospital. A final regression model was performed for a cohort of men who received radiotherapy to estimate the likelihood of receiving HDR-BT according to whether these services were regionally available.

Missing data for ethnicity (6.6%), Charlson score (8.0%), T-stage (1.6%), N-stage (6.7%), Gleason score (26.3%) and PSA (19.9%) were imputed with statistical imputation using chained equations to create ten data sets. Rubin's rules were then used to combine the risk ratios across all ten data sets.

Results

79,085 newly diagnosed patients were identified from the NPCA database between April 1st 2014 and March 31st 2016. 1495 men (1.9%) and 7840 men (9.9%) were excluded as there was insufficient information available to ascertain their diagnosing hospital or cancer stage, respectively. The patient cohort was further restricted to a final cohort of 27,248 men (48.8%) with high-risk or locally advanced prostate cancer (Fig. 1).

Most men (56.3%) were diagnosed at a spoke hospital (Table 1). There was no significant difference in the characteristics of those diagnosed at a hub or spoke hospital (age, ethnicity, socioeconomic deprivation status, number of co-morbidities, T stage, N stage, Gleason score and PSA).

66% of the men received radical treatment for their high-risk or locally advanced disease (Table 2). The variation between the 48 regional referral networks that co-ordinate specialist prostate cancer services ranged from 43.4% to 84.9%. Radical treatment was performed just as frequently, irrespective of whether the diagnosing hospital was a hub or a

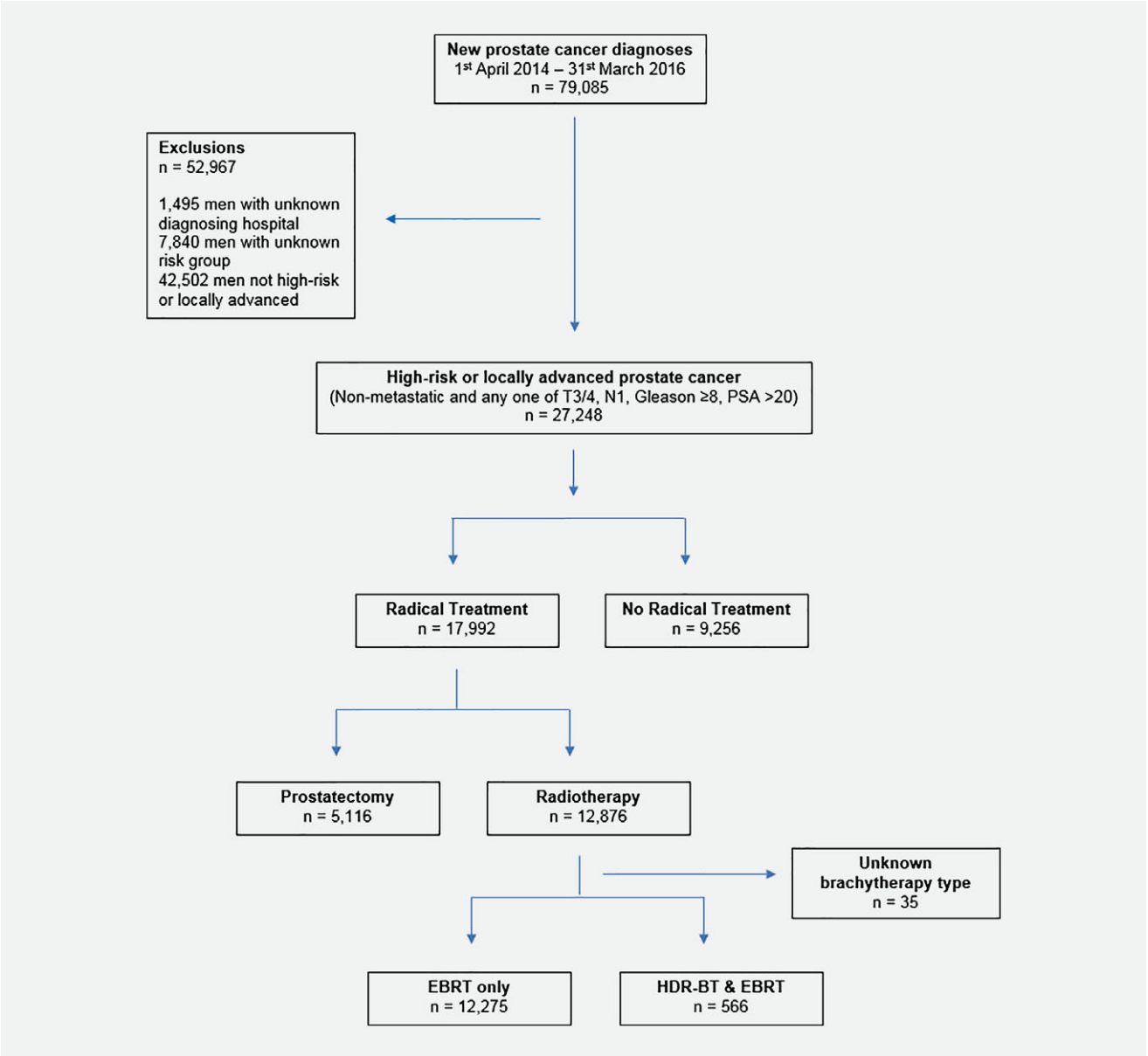

Figure 1. Flow-chart of all men with a new diagnosis of prostate cancer in England from April 1, 2014 to March 31, 2016 and how they were managed. [Color figure can be viewed at wileyonlinelibrary.com]

spoke: 8051 of 11,895 men (67.7%) who were diagnosed at a hub hospital received radical treatment, compared to 9941 of 15,353 (64.8%) who were diagnosed elsewhere (adjusted risk ratio 0.99, 95% CI 0.91 to 1.08).

Men with high-risk or locally advanced disease were less likely to receive radical treatment if they had one or more comorbidity, T1 or T4 stage, lymph node involvement, Gleason score 6, PSA >20 ng/mL, or were aged 70 years or more (p always <0.05), but there was no evidence for an association with ethnicity (Supporting Information Table 1). Although there was a trend toward decreasing socioeconomic deprivation and receipt of radical treatment, this did not reach statistical significance ($p = 0.07$).

Of the 17,992 men who received radical treatment, 5116 (28.4%) underwent surgery. RP was performed more frequently for men who were diagnosed at a hospital which provided surgical services: Of the 9199 men who were diagnosed at a hospital with these services available on-site, 2946 (32.0%) had an RP, compared to 2170 (24.7%) of the 8793 patient who were diagnosed elsewhere (adjusted risk ratio 1.24, 95% CI 1.10 to 1.40) (Table 3). Men were more likely to receive surgery as radical treatment if they had a comorbidity score ≤ 1, T2 or T3 stage, absent lymph node involvement, Gleason score ≤ 7, PSA <10 ng/mL, a lower socioeconomic deprivation score or were younger (p always <0.05). There was no evidence for an association between ethnicity and having surgery (Supporting Information Table 2).

Table 1. Patient and tumour characteristics of men with high-risk and locally advanced prostate cancer according to whether they were diagnosed at a hub or a spoke hospital.[1]

	Hub n = 11,895		Spoke n = 15,353		All men N = 27,248	
	n	%	n	%	N	%
Age group (years)						
‹65	2,571	21.6	3,038	19.8	5,609	20.6
65–70	2,703	22.7	3,333	21.7	6,036	22.2
70–75	2,625	22.1	3,287	21.4	5,912	21.7
›75	3,996	33.6	5,695	37.1	9,691	35.6
Ethnicity						
White	10,291	92.9	13,476	93.7	23,767	93.4
Black	383	3.5	419	2.9	802	3.2
Other	399	3.6	491	3.4	890	3.5
Missing	822		967		1,789	
Socioeconomic deprivation status (fifth of national distribution)						
1 (least deprived)	1,651	13.9	1,858	12.1	3,509	12.9
2	1,921	16.2	2,649	17.3	4,570	16.8
3	2,386	20.1	3,273	21.3	5,659	20.8
4	2,889	24.3	3,863	25.2	6,752	24.8
5 (most deprived)	3,048	25.6	3,710	24.2	6,758	24.8
Number of co-morbidities (RCS Charlson score)						
0	8,049	75.0	10,305	71.9	18,354	73.2
1	1,911	17.8	2,805	19.6	4,716	18.8
≥2	781	7.3	1,220	8.5	2,001	8.0
Missing	1,154		1,023		2,177	
T stage						
1	587	5.0	837	5.5	1,424	5.3
2	2,737	23.4	3,662	24.2	6,399	23.9
3	7,873	67.3	9,918	65.6	17,791	66.4
4	507	4.3	692	4.6	1,199	4.5
Missing	191		244		435	
N stage						
0	9,659	87.9	12,595	87.2	22,254	87.5
1	1,329	12.1	1,846	12.8	3,175	12.5
Missing	907		912		1,819	
Gleason score						
6	613	7.3	1,170	10.1	1,783	8.9
7	3,900	46.1	5,143	44.3	9,043	45.0
≥8	3,944	46.6	5,306	45.7	9,250	46.1
Missing	3,438		3,734		7,172	
Serum PSA (ng/mL)						
‹10	2,756	30.7	3,767	29.3	6,523	29.9
10–20	2,249	25.0	3,094	24.1	5,343	24.5
›20	3,982	44.3	5,983	46.6	9,965	45.7
Missing	2,908		2,509		5,417	

[1]Hub: hospital assigned as the lead of a regional referral network. Spoke: peripheral hospitals within the regional referral network.

35 men (5.8%) who underwent brachytherapy were excluded as there was insufficient information to differentiate between HDR-BT and low-dose rate brachytherapy (LDR-BT). Of the 12,841 men who received radiotherapy and could potentially be included, 556 (4.4%) underwent HDR-BT. HDR-BT was used more frequently in men who were diagnosed at a hospital with regional access to these services: 490 (7.7%) of the 6390 men had regional access to HDR-BT, compared to 76 (1.2%) of the 6451 men diagnosed in hospitals without regional access (adjusted risk ratio 6.16, 95% CI

Table 2. Results of Poisson regression analysis evaluating the association between the hub or spoke status of the diagnosing hospital and whether radical treatment was received for men with high-risk and locally advanced prostate cancer (n = 27,248).[1]

	Radical Treatment (%)	Adjusted RR	95% CI			P^2
Diagnosing hospital						**0.85**
Hub	67.7	1				
Spoke	64.8	0.99	0.91	-	1.08	

[1]Adjusted for age, ethnicity, socioeconomic deprivation status, RCS Charlson co-morbidity score, T stage, N stage, Gleason score, and PSA.
[2]Wald test.

Table 3. Results of Poisson regression analysis evaluating the association between the availability of surgical services on-site and whether men with high-risk and locally advanced prostate cancer who received radical treatment underwent surgery (n = 17,992).[1]

	Surgery (%)	Adjusted RR	95% CI			P^2
On-site surgery						**<0.01**
No	24.7	1				
Yes	32.0	1.24	1.10	-	1.40	

[1]Adjusted for age, ethnicity, socioeconomic deprivation status, RCS Charlson co-morbidity score, T stage, N stage, Gleason score, and PSA.
[2]Wald test.

2.94 to 12.92) (Table 4). Men were more likely to receive both HDR-BT and EBRT, over EBRT alone, if they had a co-morbidity score ≤ 1, ≤T3 stage, absent lymph node involvement, Gleason score ≤ 7, PSA 10 ng/mL to 20 ng/mL (compared to PSA >20 ng/mL), a lower socioeconomic deprivation score or were younger ($p < 0.05$ for all variables). There was no association between ethnicity or Gleason score and the receipt of HDR-BT (Supporting Information Table 3).

Discussion

The centralisation of prostate cancer services at hubs and the use of regional referral networks in England does not impact on the overall access to radical treatment for men with high-risk/locally advanced prostate cancer. However, there is variation between centres in the type of treatment selected. Men diagnosed at a hospital with surgical facilities were more likely to receive surgery than men diagnosed at a non-surgical centre. Equally, men diagnosed at a hospital where HDR-BT was regionally available were more likely to receive it.

Table 4. Results of Poisson regression analysis evaluating the association between the regional availability of high dose rate brachytherapy (HDR-BT) services and whether men with high-risk and locally advanced prostate cancer who received radical radiotherapy also received HDR-BT (n = 12,835).[1]

	HDR-BT (%)	Adjusted RR	95% CI			P^2
HDR-BT available						**<0.01**
No	1.2	1				
Yes	7.7	6.16	2.94	-	12.92	

[1]Adjusted for age, ethnicity, socioeconomic deprivation status, RCS Charlson co-morbidity score, T stage, N stage, Gleason score, and PSA.
[2]Wald test.

Treatment practices

Our data indicates that between April 2014 and March 2016, 34% of men with high-risk or locally advanced prostate cancer did not receive radical treatment and were potentially undertreated. Latest figures show that this figure continues to drop (27% in men diagnosed between April 2016 and March 2017) but in general these men represent older and more co-morbid or frail patients where radical treatment is contraindicated.[4] These observations are generally consistent with other developed countries where rates of under-treatment are reported at 32% in France (2011)[25], 41% in Germany (2004 to 2012)[26] and 15% in the US (2004 to 2013).[26,27]

EBRT remains the most common primary treatment modality in the UK for the treatment of high-risk or locally advanced prostate cancer (47% had EBRT and 19% surgery). These figures are consistent with the most recent NPCA data (2015/2016) where 49% had EBRT and 22% had surgery.[4] There is currently no clear evidence in favour of using primary RP for these cases but observations from other high-income countries indicate that RP is used more frequently for this patient group (RP 43% and EBRT 42% in the US; RP 37% and EBRT 22% in Germany).[26] Comparisons are difficult due to different inclusion criteria but contemporary figures all indicate that the use of RP in high-risk and locally advanced men is increasing, especially within a multimodal setting.[26–29]

Cancer service centralisation

Cancer services in the UK have been centralised to high-volume centres in order to improve patient outcomes.[13,14] Our data show that the hub-and-spoke model appears to be working as men are equally as likely to receive radical treatment, irrespective of the type of hospital where they were diagnosed. This is in contrast to other centres' experience in the UK and Europe with other cancer types, where service centralisation has had the opposite effect and led to a treatment inequity between hospitals.[16,17]

Data from the US have shown that high-volume centres and hospitals treating high proportions of men with newer technologies (robotic surgery or intensity-modulated radiation therapy) are more likely to treat men radically. Comparisons between the UK and the US are complex however, due to organisational differences in cancer care.[30] US arrangements are more fragmented and less centralised which allows the type of hospital to have more of an effect on the treatment

men receive. In contrast, the creation of the 48 regional referral networks in the UK currently ensures consistent access to radical treatment irrespective of hospital type. The disparity in insurance coverage in the US also contributes to the issue of under-treatment, a problem which is avoided in the UK due to the benefits of a universal healthcare system.[30,31]

Treatment selection—HDR-BT

Combining HDR-BT and EBRT for the treatment of high-risk prostate cancer improves biochemical control over EBRT alone, and it has been included in NICE guidelines since 2014.[5,32] Randomised data is lacking regarding its survival advantage, whereas observational data, including their collation in a meta-analysis, has suggested its superiority.[10,32,33] Despite the growing evidence in support of HDR-BT for high-risk disease, literature is lacking regarding the uptake and availability of this modality in the UK. Only 19 hospitals in England provide HDR-BT services and, of the 12,841 men who underwent radiotherapy in the study period, only 4.4% received multimodal treatment with HDR-BT.

Men were more likely to receive HDR-BT if they were diagnosed at a hospital where it was regionally available, indicating a huge disparity in treatment access. The US has seen declining rates of brachytherapy use, with and without EBRT, and it has been suggested that this is due to changes in referral patterns, advances with alternative therapies or the lack of adequate training.[27] These explanations highlight similarities with our findings where the availability of HDR-BT services is limited to only half of the regional referral networks in England. Expansion of HDR-BT services at other radiotherapy centres across the UK, with additional communication channels between regional referral networks, may improve access in the future.

Treatment selection—surgery

Although service centralisation does not appear to affect access to radical treatment, we have shown that men diagnosed at surgical centres were more likely to undergo radical prostatectomy than those diagnosed elsewhere. This finding was also observed in the US where patients seen at community hospitals, as opposed to high-volume academic institutions or cancer centres, were less likely to have surgery as their initial treatment.[27]

Specialty bias is well documented where physicians and surgeons tend to recommend treatments that they themselves are trained to deliver. In prostate cancer, surgeons are more likely to recommend RP than non-surgeons.[34,35] This bias can be extrapolated to sub-specialty urology whereby urologists who are sub-specialists in pelvic oncology, and work at specialist centres, may be more likely to recommend RP for higher risk men than generalists who adhere to the standard of care. Specialists may be also less risk averse to operating on more elderly patients or men with multiple co-morbidities. Although service centralisation leads to differences in treatment selection between hospitals, clearly this is a multifactorial process involving the complex interplay of patient, clinician, hospital, geographical, socioeconomic and financial factors, where all factors should be taken into account as part of the decision-making process.[35]

Strengths and limitations

Strengths of this population-based study include the high volume of patients included. Data on all men newly diagnosed with prostate cancer are collected by NCRAS and so helps to limit potential selection bias of our study cohort.

A further strength of our study is the accuracy of the routinely collected data used which has been shown to be sufficiently high to support its use for research.[36] It was not possible to differentiate between men who did not have radical treatment and those with missing treatment information. However, this misclassification is likely to be minimal, given the coding completeness, and non-differential between comparator groups, given that the primary purpose of the administrative data used is for reimbursement, and would therefore only lead to an underestimation of the effect. In addition, a validated method was used to identify co-morbidities in the HES record which aids the validity of our adjusted study estimates.[20]

Limitations include the selection bias due to the exclusion of men with an unknown diagnosing hospital (1.9%) or risk group (9.9%). However, the amount of missing data was modest in relation to the overall study size and we therefore feel that the findings remain representative. A further limitation is that because we were using available existing data there was no information on the reasons why men did not undergo radical treatment. Factors may include patient preference, path to diagnosis (PSA testing or symptomatic presentation), travel times, frailty or treatment contraindications, and without adjusting for these factors the value of the term 'under-treatment' has to be interpreted with caution. Equally there are important risk factors which are not routinely collected, such as family history, and may further influence treatment practices.

Conclusions

The centralisation of prostate cancer services does not affect the decision to treat men with high-risk or locally advanced prostate cancer radically. However, the provision of surgical services or specialist HDR-BT units at specific hospitals in England appears to cause differences in treatment selection. Discussions within regional referral networks seem to be focused on whether or not to offer radical treatment but the type of treatment selected remains left to those directly involved in the patient's management. More specifically, the limited regional availability of HDR-BT is likely to be preventing its selection in specific geographical areas of England.

To ensure patient-centred care, more attention should be given to the type of treatment men receive and ensure that all

potential options are considered when newly diagnosed men are discussed within the specialist MDT of a regional referral network. This is particularly relevant for fit, elderly patients where radical treatment may be a good option. Also, access to the HDR-BT services needs to be expanded and inter-region referral pathways established, so these services are more widely available for patients.

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Author contributions

M.G.P. designed the work, analysed and interpreted the data, drafted the article and approved the final version to be published. A.S. designed the work, analysed and interpreted the data, provided critical revision and approved the final version to be published. T.C. analysed and interpreted the data, provided critical revision and approved the final version to be published. J.N. provided critical revision and approved the final version to be published. P.C. provided critical revision and approved the final version to be published. A.A. designed the work, analysed and interpreted the data, provided critical revision and approved the final version to be published. N.W.C. provided critical revision and approved the final version to be published. H.P. provided critical revision and approved the final version to be published. J.v.d.M. designed the work, analysed and interpreted the data, contributed to the drafting of the article, and approved the final version to be published.

Ethics Approval

All patient data used is fully anonymised and is therefore exempt from UK National Research Ethics Committee (NREC) approval.

Availability of Data and Materials

The cancer registry data used for our study are based on information collected and quality assured by Public Health England's National Cancer Registration and Analysis Service (www.ncras.nhs.uk). Access to the data was facilitated by the Public Health England's Office for Data Release. Hospital Episode Statistics were made available by the NHS Health and Social Care Information Centre (© 2012; re-used with the permission of NHS Digital (www.digital.nhs.uk); all rights reserved).

References

1. National Prostate Cancer Audit. Third Year Annual Report - Results of the NPCA Prospective Audit and Patient Survey (2016). Available at: http://www.npca.org.uk/annual-report-2016/ (accessed February 16, 2018).
2. Payne H. Management of locally advanced prostate cancer. *Asian J Androl* 2009;11:81–7.
3. Tomioka A, Tanaka N, Yoshikawa M, et al. Risk factors of PSA progression and overall survival in patients with localized and locally advanced prostate cancer treated with primary androgen deprivation therapy. *BMC Cancer* 2015;15:420.
4. National Prostate Cancer Audit. Annual Report 2017: Results of the NPCA Prospective Audit in England and Wales for men diagnosed from 1 April 2015–31 March 2016 (2018). Available at: http://www.npca.org.uk/content/uploads/2017/11/NPCA-2017-Annual-Report_final_211117.pdf (accessed Spetember 9, 2018).
5. National Institute for Health and Care Excellence. Prostate cancer: diagnosis and management (2014). Available at: http://www.nice.org.uk/guidance/CG175 (accessed February 16, 2018).
6. Warde P, Mason M, Ding K, et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. *Lancet* 2011;378:2104–11.
7. Widmark A, Klepp O, Solberg A, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. *Lancet* 2009;373:301–8.
8. James ND, Spears MR, Clarke NW, et al. Failure-free survival and radiotherapy in patients with newly diagnosed nonmetastatic prostate cancer: data from patients in the control arm of the STAMPEDE trial. *JAMA Oncol* 2016;2:348–57.
9. European Association of Urology. Guidelines on Prostate Cancer (2017). Available at: http://uroweb.org/guideline/prostate-cancer/ (accessed February 16, 2018).
10. Kishan AU, Cook RR, Ciezki JP, et al. Radical prostatectomy, external beam radiotherapy, or external beam radiotherapy with brachytherapy boost and disease progression and mortality in patients with Gleason score 9-10 prostate cancer. *JAMA* 2018;319:896–905.
11. Veeratterapillay R, Goonewardene SS, Barclay J, et al. Radical prostatectomy for locally advanced and metastatic prostate cancer. *Ann R Coll Surg Engl* 2017;99:259–64.
12. European Association of Urology. Guidelines on Prostate Cancer (2016). Available at: http://uroweb.org/wp-content/uploads/EAU-Guidelines-Prostate-Cancer-2016.pdf (accessed February 16, 2018).
13. National Institute for Clinical Excellence. Guidance on cancer services: improving outcomes in urological cancers (2002). Available at: http://www.nice.org.uk/guidance/csg2/resources/improving-outcomes-in-urological-cancers-pdf-773372413 (accessed February 16, 2018).
14. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med* 2002;346:1128–37.
15. Aggarwal A, Nossiter J, Cathcart P, et al. Organisation of prostate cancer Services in the English

National Health Service. *Clin Oncol (R Coll Radiol)* 2016;28:482–9.
16. Khakwani A, Rich AL, Powell HA, et al. The impact of the 'hub and spoke' model of care for lung cancer and equitable access to surgery. *Thorax* 2015;70:146–51.
17. Vallance AE, Vandermeulen J, Kuryba A, et al. Impact of hepatobiliary service centralization on treatment and outcomes in patients with colorectal cancer and liver metastases. *Br J Surg* 2017; 104:918–25.
18. National Health Service. Hospital Episode Statistics. Available at: http://www.hesonline.nhs.uk (accessed 5 January 2018, 2017).
19. National Cancer Registration and Analysis Service. National Radiotherapy Dataset (RTDS). Available at: http://www.ncin.org.uk/collecting_and_using_data/rtds (accessed 11 December, 2017).
20. Armitage JN, van der Meulen JH. Identifying comorbidity in surgical patients using administrative data with the Royal College of surgeons Charlson score. *Br J Surg* 2010;97:772–81.
21. Noble M, McLennan D, Wilkinson K, et al. The English Indices of Deprivation 2007. Available at: http://geoconvert.mimas.ac.uk/help/imd-2007-manual.pdf (accessed 28 September 2017, 2017).
22. NHS Digital. NHS Classifications Service: OPCS Classifications of Interventions and Procedures Version 4.4; 2007. Available at: http://systems.digital.nhs.uk/data/clinicalcoding/codingstandards/opcs4 (accessed 28 September, 2017).
23. Knol MJ, Le Cessie S, Algra A, et al. Overestimation of risk ratios by odds ratios in trials and cohort studies: alternatives to logistic regression. *CMAJ* 2012;184:895–9.
24. Gutierrez RG. Parametric frailty and shared frailty survival models. *Stata J* 2002;2:22–44.
25. Lunardi P, Ploussard G, Grosclaude P, et al. Current impact of age and comorbidity assessment on prostate cancer treatment choice and over/-undertreatment risk. *World J Urol* 2017;35: 587–93.
26. Hager B, Kraywinkel K, Keck B, et al. Increasing use of radical prostatectomy for locally advanced prostate cancer in the USA and Germany: a comparative population-based study. *Prostate Cancer Prostatic Dis* 2016;20:61–6.
27. Weiner AB, Matulewicz RS, Schaeffer EM, et al. Contemporary management of men with high-risk localized prostate cancer in the United States. *Prostate Cancer Prostatic Dis* 2017;20: 283–8.
28. Trama A, Botta L, Nicolai N, et al. Prostate cancer changes in clinical presentation and treatments in two decades: an Italian population-based study. *Eur J Cancer* 2016;67:91–8.
29. Cooperberg MR, Broering JM, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. *J Clin Oncol* 2010;28: 1117–23.
30. Gerhard RS, Patil D, Liu Y, et al. Treatment of men with high-risk prostate cancer based on race, insurance coverage, and access to advanced technology. *Urol Oncol* 2017;35:250–6.
31. Mahal BA, Chen YW, Muralidhar V, et al. National sociodemographic disparities in the treatment of high-risk prostate cancer: do academic cancer centers perform better than community cancer centers? *Cancer* 2016;122:3371–7.
32. Hoskin PJ, Rojas AM, Bownes PJ, et al. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. *Radiother Oncol* 2012;103:217–22.
33. Pieters BR, de Back DZ, Koning CC, et al. Comparison of three radiotherapy modalities on biochemical control and overall survival for the treatment of prostate cancer: a systematic review. *Radiother Oncol* 2009;93:168–73.
34. Fowler FJ Jr, McNaughton Collins M, Albertsen PC, et al. Comparison of recommendations by urologists and radiation oncologists for treatment of clinically localized prostate cancer. *JAMA* 2000;283:3217–22.
35. Zeliadt SB, Ramsey SD, Penson DF, et al. Why do men choose one treatment over another?: a review of patient decision making for localized prostate cancer. *Cancer* 2006;106:1865–74.
36. Burns EM, Rigby E, Mamidanna R, et al. Systematic review of discharge coding accuracy. *J Public Health (Oxf)* 2012;34:138–48.

6 PELVIC LYMPH NODE IRRADIATION

6.1 Research Paper 4

Title: Treatment-related toxicity using prostate-only versus prostate and pelvic lymph node intensity-modulated radiation therapy: a national population-based study.

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Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	LSH1800100	**Title**	Dr
First Name(s)	Matthew		
Surname/Family Name	Parry		
Thesis Title	Use of routinely collected hospital data to explore access to and outcomes from different radiotherapy treatment strategies for locally advanced prostate cancer: national population-based studies.		
Primary Supervisor	Professor Jan van der Meulen		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Journal of Clinical Oncology		
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SECTION E

Student Signature	M. Parry
Date	8/1/21

Supervisor Signature	J. van der Meulen
Date	8/1/21

original report

Treatment-Related Toxicity Using Prostate-Only Versus Prostate and Pelvic Lymph Node Intensity-Modulated Radiation Therapy: A National Population-Based Study

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abstract

PURPOSE There is a debate about the effectiveness and toxicity of pelvic lymph node (PLN) irradiation for the treatment of men with high-risk prostate cancer. This study compared the toxicity of intensity-modulated radiation therapy (IMRT) to the prostate and the pelvic lymph nodes (PPLN-IMRT) with prostate-only IMRT (PO-IMRT).

MATERIALS AND METHODS Patients with high-risk localized or locally advanced prostate cancer treated with IMRT in the English National Health Service between 2010 and 2013 were identified by using data from the Cancer Registry, the National Radiotherapy Dataset, and Hospital Episode Statistics, an administrative database of all hospital admissions. Follow-up was available up to December 31, 2015. Validated indicators were used to identify patients with severe toxicity according to the presence of both a procedure code and diagnostic code in patient Hospital Episode Statistics records. A competing risks regression analysis, with adjustment for patient and tumor characteristics, estimated subdistribution hazard ratios (sHRs) by comparing GI and genitourinary (GU) complications for PPLN-IMRT versus PO-IMRT.

RESULTS Three-year cumulative incidence in the PPLN-IMRT (n = 780) and PO-IMRT (n = 3,065) groups was 14% for both groups for GI toxicity, and 9% and 8% for GU toxicity, respectively. Patients receiving PPLN-IMRT and PO-IMRT had similar levels of severe GI (adjusted sHR, 1.00; 95% CI, 0.80 to 1.24; $P = .97$) and GU (adjusted sHR, 1.10; 95% CI, 0.83 to 1.46; $P = .50$) toxicity rates.

CONCLUSION Including PLNs in radiation fields for high-risk or locally advanced prostate cancer is not associated with increased GI or GU toxicity at 3 years. Additional follow-up is required to answer questions about its impact on late GU toxicity. Results from ongoing trials will provide insight into the anticancer effectiveness of PLN irradiation.

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INTRODUCTION

The combination of prostate radiotherapy (RT) with androgen deprivation therapy is well established as treatment for intermediate-risk, high-risk, and locally advanced prostate cancer.[1] One particular area of interest for RT is whether pelvic lymph nodes (PLNs) should be included in radiation fields for high-risk cases. In the United Kingdom, the National Institute for Health and Care Excellence currently recommends PLN irradiation only for patients with a high risk of nodal involvement, but there is no clear standard to follow.[1]

All randomized controlled trials (RCTs) to date have shown no clinically important differences in cancer outcomes. However, several limitations have been highlighted, such as the inclusion of low-risk men and differences in duration of hormonal treatment.[2-4] The recent update of the Radiation Therapy Oncology Group RTOG-9413 trial demonstrates the benefit of PLN irradiation at 10 years but only when it is used alongside neoadjuvant hormone therapy, which represents an important but somewhat unusual interaction between field size and neoadjuvant or adjuvant hormone use.[4,5] It is also important to note that those trials were conducted before the dose-escalation era by using conventional four-field or 3D-conformal techniques, which are becoming more and more outdated in prostate cancer. Results from three RCTs that used intensity-modulated radiation therapy (IMRT) and dose escalation are awaited to confirm the effectiveness of PLN irradiation in achieving cancer control.[6-8]

External beam RT to the prostate gland is associated with both GI and genitourinary (GU) complications. However, results are mixed regarding whether the addition of PLN irradiation, and consequently the inclusion of a larger volume of normal tissue in the

Author affiliations and support information (if applicable) appear at the end of this article.

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treatment field, confers worse toxicity. Studies to date have been relatively small, and until recently, IMRT was not used.[3,5,9-16] Because IMRT is now the accepted standard for primary prostate RT, historic data on the effectiveness and toxicity after 3D-conformal techniques have limited value.[17] There is currently no comparative data on how PLN-IMRT affects toxicity.

PLN irradiation features in contemporary guidelines for selected high-risk prostate cancer cases. Thus, knowledge of treatment toxicity is particularly important, given the ongoing debate surrounding its optimal use.[1] For this study, we used linked national data sets to quantify how prostate and pelvic lymph node IMRT (PPLN-IMRT) alters the toxicity that patients' experience compared with those who receive prostate-only IMRT (PO-IMRT).

MATERIALS AND METHODS

Patient Population

This study used English Cancer Registry data,[18] the National Radiotherapy Dataset (RTDS),[19] and Hospital Episode Statistics (HES),[20] linked at the patient level to observe men who were diagnosed with prostate cancer and treated with radical RT between January 1, 2010, and December 31, 2013. The International Classification of Diseases 10th Edition[21] code C61 was used to identify men with prostate cancer in the cancer registry data set.

In all, 10,569 men receiving IMRT for nonmetastatic prostate cancer were identified using the Office of Population Censuses and Surveys Classification of Interventions and Procedures Version 4 code X671[22] in the RTDS. The cohort was stratified according to a modified D'Amico risk stratification algorithm developed previously by the National Prostate Cancer Audit to account for the absence of prostate-specific antigen information.[17] Figure 1 shows exclusions, which resulted in a final cohort of 3,845 men with high-risk or locally advanced prostate cancer.

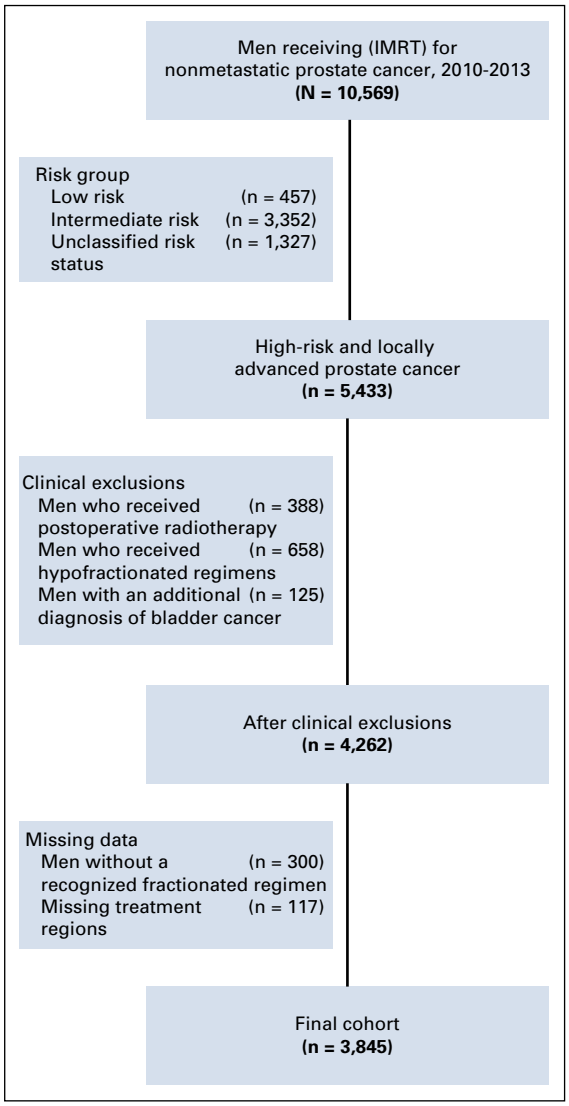

FIG 1. Flowchart of patients included in study. IMRT, intensity-modulated radiation therapy.

Study Outcome

We used previously validated performance indicators to identify men who experienced any urinary or bowel-related toxicity after RT that was severe enough to require a diagnostic or therapeutic procedure.[23] GI or GU toxicity was defined as the presence of both a diagnostic code, according to the International Classification of Diseases 10th Edition,[21] and a procedure code, according to the Office of Population Censuses and Surveys Classification of Surgical Interventions and Procedures Version 4,[22] in a patient's HES record that were related to complications after RT. This is comparable to at least grade 3 toxicity, according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE).[24] GU toxicity included a procedure of the lower urinary tract alongside a diagnosis of either hematuria, cystitis, GU obstruction, retention, stricture, or incontinence. GI toxicity included an endoscopic procedure or an anal or peri-anal operation alongside a relevant diagnosis for gastroenteritis, colitis, proctitis, lower GI fistula, stenosis, ulcer, or hemorrhage. The primary outcomes were the proportion of men experiencing a GI or GU complication from the date of their initial RT. Patients were observed until December 31, 2015. Baseline GI and GU function was estimated on the basis of the presence of a GI or GU procedure code in the HES record up to 1 year before the start of RT.[23]

Explanatory and Control Variables

The RTDS was used to provide information on the RT field (PO and PPLN). Given that PPLN-RT is usually divided into a PPLN dose and a PO boost dose, it was only possible to ascertain the total PPLN dose and not the isolated dose delivered to the PLNs. Data items in the HES records were used to determine age, comorbidities, and socioeconomic deprivation status. The Royal College of Surgeons Charlson score was used to identify any comorbid conditions coded

in the HES records within 1 year of diagnosis.[25] Socioeconomic deprivation status was determined for patients from the English 2012 Index of Multiple Deprivation on the basis of their area of residence and divided according to quintiles of the national distribution.[26] T stage, N stage, M stage, and Gleason score were identified from the Cancer Registry data to enable disease staging.

Statistical Analysis

We compared patient and tumor characteristics at baseline using χ^2 tests. The 3-year cumulative incidences of both GI and GU complications were calculated by using a competing risks method in which death was the competing event.[27] We also calculated incidence rates using total events per 100 person-years, which took account of death as the competing event.

A competing risks regression analysis, according to Fine and Gray[28] via maximum likelihood, was used to estimate subdistribution hazard ratios (sHRs) with 95% CIs comparing the risk of GI or GU complications between PO-IMRT and PPLN-IMRT groups. Men were censored at the end of follow-up, and the regression analysis was adjusted for patient and tumor characteristics. Missing values for deprivation status (n = 31), T stage (n = 188), N stage (n = 723), and Gleason score (n = 104) were imputed using multiple imputation by chained equations. In all, 50 data sets were created, and Rubin's rules were used to combine the sHRs. Wald tests were used to calculate *P* values with significance set at $P < .05$.

RESULTS

Patient Population

Of the 3,845 included men with high-risk or locally advanced prostate cancer who received IMRT between 2010 and 2013, 20% (n = 780) received PLN irradiation (Table 1). The median age was 70 years (range, 44 to 88 years), and 21% had at least one comorbidity. The presence of specific comorbidities associated with anticoagulation use (myocardial infarction, peripheral vascular disease, and cerebrovascular disease) did not vary between PO-IMRT and PPLN-IMRT groups. In total, 75% had T3/T4 disease, 13% had N1 disease, and 61% had a Gleason score of 8 or greater. The median dose per fraction and total dose to the prostate were the same in both groups (2 Gy per fraction and 74 Gy, respectively). Men receiving PPLN-IMRT were more likely to be aged 70 years or younger, to be more socioeconomically deprived, and to have more advanced disease (T3/T4 disease, N1 disease and a Gleason score of 8 or greater) than men receiving PO-IMRT. Baseline measures of GI and GU procedures up to 1 year before RT were similar between study groups. Follow-up time was defined as the time to the end of follow-up for men who were still alive and free from GI or GU toxicity. Median follow-up was 2.7 years for all men, 2.7 years for the PPLN-IMRT group, and 2.6 years for the PO-IMRT group.

Outcome Measures

Although GI complications were rare in the first 9 months, cumulative incidence curves show that both GI and GU toxicity were similar between the study groups throughout the study period (Figs 2 and 3). The 3-year cumulative incidence of GI complications was 14% (95% CI, 11% to 17%) in men who had PPLN-IMRT and 14% (95% CI, 13% to 15%) in men who had PO-IMRT. Men experienced 4.9 (95% CI, 4.0 to 5.9) GI complications per 100 person-years in the PPLN-IMRT group compared with 5.1 (95% CI, 4.6 to 5.6) in the PO-IMRT group. The 3-year cumulative incidence of GU toxicity was also comparable with 9% (95% CI, 7% to 11%) in the PPLN-IMRT group and 8% (95% CI, 7% to 9%) in the PO-IMRT group. Men experienced 3.2 (95% CI, 2.5 to 4.0) GU complications per 100 person-years in the PPLN-IMRT group compared with 2.7 (95% CI, 2.4 to 3.1) in the PO-IMRT group (Table 2).

An adjusted competing risk regression analysis showed that the incidence of GI toxicity in men receiving PPLN-IMRT was similar to that in patients receiving PO-IMRT (sHR, 1.00; 95% CI, 0.80 to 1.24; $P = .97$). GU toxicity was also similar between the two groups (sHR, 1.10; 95% CI, 0.83 to 1.46; $P = .50$; Table 2). There was no significant difference in toxicity rates according to age, treatment year, T stage, N stage, or Gleason score (Data Supplement).

Men with at least one comorbidity were more likely to experience GU toxicity than men with no comorbidities (sHR, 1.39; 95% CI, 1.07 to 1.79; $P = .01$), but there was no statistically significant effect of comorbidity on the GI toxicity rate (sHR, 1.18; 95% CI, 0.97 to 1.45; $P = .11$). In addition, men in the highest quintile of socioeconomic deprivation (most deprived) had lower GI toxicity compared with men in the lowest quintile (least deprived) (sHR, 0.68; 95% CI, 0.49 to 0.96; $P = .01$) but no such effect was observed for GU toxicity (Data Supplement).

DISCUSSION

The results indicate that the risk of severe GI or GU toxicity does not vary between patients receiving PPLN-IMRT and those receiving PO-IMRT. Within 3 years of IMRT, 14% of patients experienced severe grade 3 GI toxicity, and 8% experienced severe grade 3 GU toxicity (CTCAE), irrespective of whether the PLNs were included in the radiation field.

Previous studies in this area are limited, and their results are conflicting. Two RCTs have compared the toxicity of PO-RT with PPLN-RT and they had different results. The RTOG-9413 RCT, which included 1,323 patients and published its results at various time points (2006, 2007, and 2018), showed that PPLN irradiation compared with PO irradiation was associated with an increase in acute grade 2 GI and GU toxicity (47% vs 20% and 31% vs 22%,

TABLE 1. Patient, Tumor, and Treatment Characteristics for Those With High-Risk or Locally Advanced Prostate Cancer Receiving IMRT

	All Patients (N = 3,845)		PO-IMRT (n = 3,065)		PPLN-IMRT (n = 780)		
Characteristic	**No.**	**%**	**No.**	**%**	**No.**	**%**	***P***
Age group, years							< .01
< 65	299	7.8	204	6.7	95	12.2	
65-70	602	15.7	445	14.5	157	20.1	
70-75	2,091	54.4	1,693	55.2	398	51.0	
> 75	853	22.2	723	23.6	130	16.7	
No. of comorbidities (RCS Charlson score)							.93
0	3,032	78.9	2,416	78.8	616	79.0	
≥ 1	813	21.1	649	21.2	164	21.0	
Deprivation status (national quintiles)							.01
1 (least deprived)	932	24.4	712	23.5	220	28.2	
2	962	25.2	778	25.6	184	23.6	
3	822	21.6	674	22.2	148	19.0	
4	604	15.8	467	15.4	137	17.6	
5 (most deprived)	494	13.0	404	13.3	90	11.6	
Missing	31		30		1		
T stage							< .01
1	250	6.8	214	7.3	36	5.1	
2	682	18.7	574	19.5	108	15.2	
3	2,623	71.7	2,093	71.1	530	74.5	
4	102	2.8	65	2.2	37	5.2	
Missing	188		119		69		
N stage							< .01
0	2,706	86.7	2,285	90.2	421	71.6	
1	416	13.3	249	9.8	167	28.4	
Missing	723		531		192		
Gleason score							< .01
6	191	5.1	166	5.6	25	3.3	
7	1,257	33.6	1,041	34.9	216	28.5	
8	968	25.9	798	26.8	170	22.4	
9	1,263	33.8	932	31.3	331	43.6	
10	62	1.7	45	1.5	17	2.2	
Missing	104		83		21		
Treatment year							< .01
2010	140	3.6	85	2.8	55	7.1	
2011	322	8.4	234	7.6	88	11.3	
2012	897	23.3	736	24.0	161	20.6	
2013	2,486	64.7	2,010	65.6	476	61.0	
GI procedure 1 year before RT							.14
No	3,639	94.6	2,909	94.9	730	93.6	
Yes	206	5.4	156	5.1	50	6.4	
GU procedure 1 year before RT							.06
No	3,224	83.9	2,587	84.4	637	81.7	
Yes	621	16.2	478	15.6	143	18.3	

Abbreviations: GU, genitourinary; IMRT, intensity-modulated radiation therapy; PO, prostate only; PPLN, prostate and the pelvic lymph nodes; RCS, Royal College of Surgeons; RT, radiation therapy.

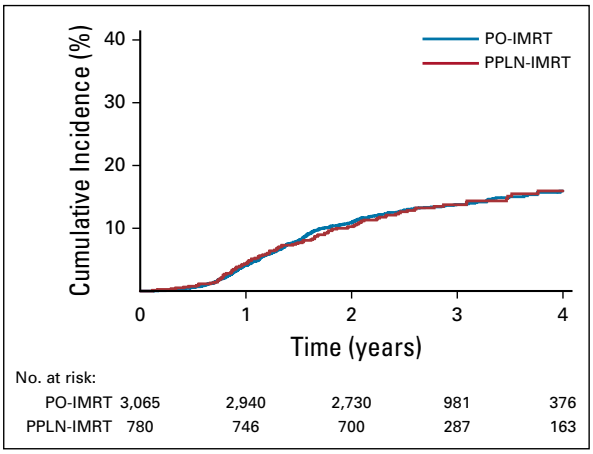

FIG 2. Cumulative incidence curves for GI toxicity after intensity-modulated radiation therapy (IMRT) to the prostate only (PO) or the prostate and pelvic lymph nodes (PPLNs).

respectively) and late grade 3 GI toxicity (7% vs 2%), according to the RTOG scale.[4,5,16] In contrast, the Groupe Etude des Tumeurs Uro Genitales GETUG-01 RCT, which included 444 patients and was published in 2007, observed similar toxicity (according to the RTOG, Late Effects Normal Tissue Task Force, and Subjective, Objective, Management, Analytic scales), in which the observed increase in grade 2 GI toxicity with PPLN-RT was nonsignificant.[3] A cohort study of 358 patients also showed similar levels of toxicity.[13] In contrast to our study, these studies included patients treated with older conformal techniques, and therefore the relevance of their results are limited in their ability to inform the toxicity risk for patients treated with IMRT.

A further cohort study of 277 patients, published in 2009, was the first to include IMRT to treat the prostate but the older four-field technique was still used for the PLNs. The

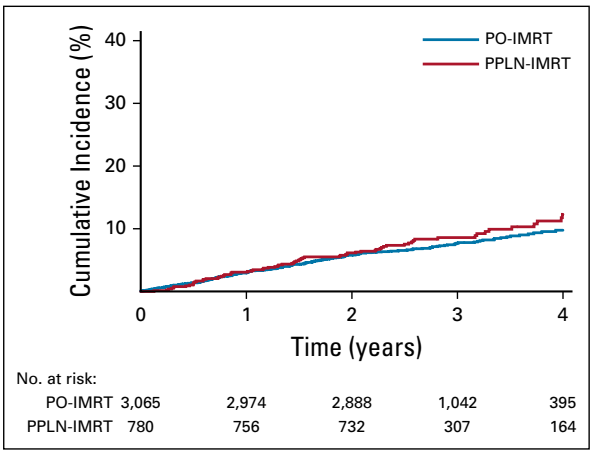

FIG 3. Cumulative incidence curves for genitourinary toxicity after intensity-modulated radiation therapy (IMRT) to the prostate only (PO) or the prostate and pelvic lymph nodes (PPLNs).

study authors reported an increased rate of acute GI toxicity (CTCAE) with PPLN-RT (75% vs 49% for grade 1 and 18% vs 7% for grade 2).[9] There was no difference in late toxicity (90 days or more) after a median of 30 months, and severe toxicity was rare with only one patient experiencing late grade 3 toxicity. With exclusively IMRT and a much larger patient population, our findings indicate that severe toxicity (grade 3 or greater) is much more prevalent, and they highlight the strength of using robust outcome measures from routine data over the potential under-reporting of clinical measures.

Initial, small-scale, noncomparative reports of PPLN-IMRT of 40 and 70 patients have shown its favorable tolerability with no severe toxicity observed (acute or late).[10,11] Results from a PPLN-IMRT dose-escalation study of 447 patients further indicate its safety.[15] The authors found similar GI toxicity (grade 2 or greater) compared with the toxicity observed in men undergoing PO-IMRT in other study cohorts.

Several studies have used patient-reported outcome measures (PROMs) to compare toxicity in men undergoing PPLN-RT or PO-RT. First, the GETUG-01 RCT found that quality of life, according to PROMs taken at 12 and 24 months after conformal RT, was similar in both groups.[3] Second, a prospective matched-pair cohort study of 120 patients (published in 2011) used the Expanded Prostate Cancer Index-26 (EPIC-26) questionnaire 16 months after conformal RT. The study found that bowel function scores were eight points lower on a scale from 0 to 100 in the PLN group than in the PO group and, although this was statistically significant, it did not represent a clinically significant difference.[14] Third, a PROMs cohort study of 120 patients (published in 2014) compared patients who had PLN-IMRT in addition to conventional conformal RT to the prostate with those who had PO-RT. According to the University of California, Los Angeles Prostate Cancer Index, urinary and bowel function were worse for the PPLN group at 3 months, but they were comparable by 12 months.[12] This likely represents an increase in mild or moderate toxicity in the acute period with PPLN-RT that resolves over time. Our results indicate that in a large United Kingdom population with national coverage, not only is the 3-year risk of severe GI and GU toxicity the same, irrespective of treatment region, but the cumulative incidence as a function of time from the start of treatment is also similar.

Strengths of this population-based study include the relatively high volume of patients (n = 3,845), making it the largest comparative study to date assessing the toxicity of PPLN-RT and, to our knowledge, the first to include IMRT exclusively. Findings are also representative of real-world practice across England because our data included all National Health Service RT providers in the country. Patients who underwent RT in the private sector were not

TABLE 2. Adjusted Outcomes for GI and GU Toxicity After PO-IMRT or PPLN-IMRT

Toxicity Site	3-Year Cumulative Incidence (%)	95% CI	Rate (total events/100 person-years)	sHR	95% CI	*P*
GI toxicity						
PO-IMRT	13.8	12.6 to 15.2	5.05	1		—
PPLN-IMRT	13.8	11.4 to 16.5	4.89	1.00	0.80 to 1.24	.97
GU toxicity						
PO-IMRT	7.7	6.7 to 8.8	2.70	1		—
PPLN-IMRT	8.6	6.7 to 10.9	3.16	1.10	0.83 to 1.46	.50

Abbreviations: GU, genitourinary; IMRT, intensity-modulated radiation therapy; PO, prostate only; PPLN, prostate and the pelvic lymph node; sHR, subdistribution hazard ratio.

included, but they represent less than 10% of the case load nationally.[29]

The indicators we used have been specifically developed and validated to identify RT-related complications severe enough to require a procedure (grade 3 or greater), which allowed us to measure toxicity at a specific severity level. The use of both diagnosis and procedure codes improved the validity of our indicators allowing us to better identify true toxicity. Previous studies using routine data, comparing IMRT with conformal RT, were limited by their use of only individual diagnosis, procedure, or claim codes to report toxicity.[30-32] Other strengths include the validated method to identify comorbidities in the HES record, which aids the reliability of our adjusted study estimates.[25] In addition, adjustments for previous GI and GU procedures allowed us to account for baseline procedures, which is often problematic when using routine data. All regression analyses were therefore adjusted for potential measurable confounders. Residual confounding could still be present, but given the small impact of adjusting for a wide range of confounders, this is likely to be minimal. Specific examples of unmeasurable factors associated with increased toxicity include anticoagulant use and treatment volumes, but because they are unlikely to vary between study groups, the potential bias from their exclusion is small.

The data collected in the RTDS was detailed regarding RT doses and patient attendances. We therefore only included men with a recognized RT regimen to ensure that the groups were comparable. A limitation of the RTDS is that it does not provide the exact RT dose administered to the PLNs, only the overall total dose. The PLN dose can vary among patients, but given that this variation is restricted to patients who underwent PPLN-IMRT, this variation is not a confounding factor for the difference between PO-IMRT and PPLN-IMRT groups.

A final limitation is the relatively short follow-up time. We demonstrated that GU toxicity rates are similar in patients who had PPLN-IMRT and PO-IMRT at 3 years after treatment. Additional GU toxicity events are likely to occur in later years, but this will introduce differences between the groups only if the occurrence of later toxicity events depends on whether PPLN-IMRT or PO-IMRT was given. The short follow-up is a direct consequence of the inclusion of a contemporary population from 2010 onward to ensure that all patients were receiving IMRT. Using an earlier population with a longer follow-up would have included a number of patients who had 3D conformal RT, which could have confounded our results.

We did not find evidence that PPLN-IMRT leads to more severe GI and GU toxicity than PO-IMRT for men with high-risk or locally advanced prostate cancer. This indicates that PLN-RT should be considered for treating these men in line with current guidelines.[1] This is particularly relevant, given the recent evidence suggesting that the pattern of relapse after RT is more nodal-centric than previously thought, which emphasizes the importance of extending the treatment field to include the PLNs.[33] However, we do not know whether extending the radiation field leads to an increased rate of secondary malignancy. Because this long-term outcome requires more than 10 years of follow-up, we are unable to comment on this, but it is certainly an area for additional research.[34]

Advances are currently being made in this area of RT. Phase II trials have already confirmed the tolerability of dose escalation and hypofractionation in PPLN-IMRT.[15,35] More importantly, there are three RCTs being undertaken using IMRT that will confirm the definitive role of PLN irradiation in terms of cancer control, but these studies do not have sufficient statistical power to compare toxicity rates.[6-8] Observational research can provide important information on adverse effects because it is likely to meet the underlying assumption that the allocation of patients to certain groups is unrelated to the occurrence of adverse effects, given that these are often unintended and unpredictable.[36]

In conclusion, including PLNs in radiation fields for high-risk or locally advanced prostate cancer is not associated with increased GI or GU toxicity at 3 years and should be considered in this patient group. Follow-up beyond 3 years is required to answer questions about its impact on late GU toxicity. Definitive evidence in favor of better cancer control with PPLN-RT is needed to fully define its role.

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M.G.P. and A.S. contributed equally to this work as first authors. J.v.d.M. and A.A. contributed equally to this work as senior authors.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.18.02237.

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Conception and design: Matthew G. Parry, Arunan Sujenthiran, Heather Payne, Jan van der Meulen, Ajay Aggarwal

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Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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All patient data used are fully anonymized and are therefore exempt from United Kingdom National Research Ethics Committee (NREC) approval. The use of English Cancer Registry data, the National Radiation Therapy Data Set and Hospital Episode Statistics was approved by the Confidentiality Advisory Group of the NHS Health Research Authority for the purpose of national clinical audit and health service evaluation (CAG 8-03[PR9]/2013).

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REFERENCES

1. National Institute for Health and Care Excellence (NICE): Prostate Cancer: Diagnosis and Management—Clinical guideline [CG175]. January 2014. http://www.nice.org.uk/guidance/cg175
2. Asbell SO, Krall JM, Pilepich MV, et al: Elective pelvic irradiation in stage A2, B carcinoma of the prostate: Analysis of RTOG 77-06. Int J Radiat Oncol Biol Phys 15:1307-1316, 1988
3. Pommier P, Chabaud S, Lagrange JL, et al: Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Preliminary results of GETUG-01. J Clin Oncol 25:5366-5373, 2007
4. Roach M, Moughan J, Lawton CAF, et al: Sequence of hormonal therapy and radiotherapy field size in unfavourable, localised prostate cancer (NRG/RTOG 9413): Long-term results of a randomised, phase 3 trial. Lancet Oncol 19:1504-1515, 2018
5. Lawton CA, DeSilvio M, Roach M III, et al: An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: Updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. Int J Radiat Oncol Biol Phys 69: 646-655, 2007
6. National Institutes of Health: A Study of Prostate and Pelvis Versus Prostate Alone Treatment for Locally Advanced Prostate Cancer (PIVOTAL). http://clinicaltrials.gov/ct2/show/NCT01685190
7. SWOG Cancer Research Network: CTSU/RTOG-0924. https://www.swog.org/clinical-trials/ctsurtog-0924
8. NHS Health Research Authority: PIVOTALBoost. http://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/pivotalboost/
9. Aizer AA, Yu JB, McKeon AM, et al: Whole pelvic radiotherapy versus prostate only radiotherapy in the management of locally advanced or aggressive prostate adenocarcinoma. Int J Radiat Oncol Biol Phys 75:1344-1349, 2009
10. Habl G, Katayama S, Uhl M, et al: Helical intensity-modulated radiotherapy of the pelvic lymph nodes with a simultaneous integrated boost to the prostate: First results of the PLATIN 1 trial. BMC Cancer 15:868, 2015
11. Joo JH, Kim YJ, Kim YS, et al: Whole pelvic intensity-modulated radiotherapy for high-risk prostate cancer: A preliminary report. Radiat Oncol J 31:199-205, 2013

12. Lilleby W, Stensvold A, Dahl AA: Adding intensity-modulated radiotherapy to the pelvis does not worsen the adverse effect profiles compared to limited field radiotherapy in men with prostate cancer at 12-month follow-up. Acta Oncol 53:1380-1389, 2014
13. Mantini G, Tagliaferri L, Mattiucci GC, et al: Effect of whole pelvic radiotherapy for patients with locally advanced prostate cancer treated with radiotherapy and long-term androgen deprivation therapy. Int J Radiat Oncol Biol Phys 81:e721-e726, 2011
14. Pinkawa M, Piroth MD, Holy R, et al: Quality of life after whole pelvic versus prostate-only external beam radiotherapy for prostate cancer: A matched-pair comparison. Int J Radiat Oncol Biol Phys 81:23-28, 2011
15. Reis Ferreira M, Khan A, Thomas K, et al: Phase 1/2 dose-escalation study of the use of intensity modulated radiation therapy to treat the prostate and pelvic nodes in patients with prostate cancer. Int J Radiat Oncol Biol Phys 99:1234-1242, 2017
16. Roach M III, DeSilvio M, Valicenti R, et al: Whole-pelvis, "mini-pelvis," or prostate-only external beam radiotherapy after neoadjuvant and concurrent hormonal therapy in patients treated in the Radiation Therapy Oncology Group 9413 trial. Int J Radiat Oncol Biol Phys 66:647-653, 2006
17. National Prostate Cancer Audit (NPCA): Annual Report 2017: Results of the NPCA Prospective Audit in England and Wales for men diagnosed from April 1, 2015 - March 31, 2016. http://www.npca.org.uk/content/uploads/2017/11/NPCA-2017-Annual-Report_final_211117.pdf
18. National Cancer Registration and Analysis Service: National Cancer Data Repository. http://www.ncin.org.uk/collecting_and_using_data/national_cancer_data_repository/
19. National Cancer Registration and Analysis Service: National Radiotherapy Dataset (RTDS). http://www.ncin.org.uk/collecting_and_using_data/rtds
20. National Health Service: Hospital Episode Statistics (HES). http://www.hesonline.nhs.uk
21. World Health Organization: International Statistical Classification of Diseases and Related Health Problems (10th Revision), Volume 2, Instruction manual. http://www.who.int/classifications/icd/ICD10Volume2_en_2010.pdf
22. NHS Digital: OPCS Classification of Interventions and Procedures. https://digital.nhs.uk/data-and-information/information-standards/information-standards-and-data-collections-including-extractions/publications-and-notifications/standards-and-collections/scci0084-opcs-classification-of-interventions-and-procedures
23. Sujenthiran A, Nossiter J, Charman SC, et al: National population-based study comparing treatment-related toxicity in men who received intensity modulated versus 3-dimensional conformal radical radiation therapy for prostate cancer. Int J Radiat Oncol Biol Phys 99:1253-1260, 2017
24. National Institutes of Health, National Cancer Institute: Common Terminology Criteria for Adverse Events (CTCAE), Version 4, May 28, 2009. http://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf
25. Armitage JN, van der Meulen JH: Identifying co-morbidity in surgical patients using administrative data with the Royal College of Surgeons Charlson Score. Br J Surg 97:772-781, 2010
26. Noble M, mcLennan D, Wilkinson K, et al: The English Indices of Deprivation 2007. http://geoconvert.mimas.ac.uk/help/imd-2007-manual.pdf
27. Coviello V, Boggess M: Cumulative incidence estimation in the presence of competing risks. Stata J 4:103-112, 2004
28. Fine JP, Gray RJ: A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 94:496-509, 1999.
29. Aggarwal A, Lewis D, Sujenthiran A, et al: Hospital quality factors influencing the mobility of patients for radical prostate cancer radiation therapy: A national population-based study. Int J Radiat Oncol Biol Phys 99:1261-1270, 2017
30. Crandley EF, Hegarty SE, Hyslop T, et al: Treatment-related complications of radiation therapy after radical prostatectomy: Comparative effectiveness of intensity-modulated versus conformal radiation therapy. Cancer Med 3:397-405, 2014
31. Goldin GH, Sheets NC, Meyer AM, et al: Comparative effectiveness of intensity-modulated radiotherapy and conventional conformal radiotherapy in the treatment of prostate cancer after radical prostatectomy. JAMA Intern Med 173:1136-1143, 2013
32. Sheets NC, Goldin GH, Meyer AM, et al: Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. JAMA 307:1611-1620, 2012
33. De Bruycker A, De Bleser E, Decaestecker K, et al: Nodal oligorecurrent prostate cancer: Anatomic pattern of possible treatment failure in relation to elective surgical and radiotherapy treatment templates. Eur Urol [epub ahead of print on November 28, 2018]
34. Wallis CJ, Mahar AL, Choo R, et al: Second malignancies after radiotherapy for prostate cancer: systematic review and meta-analysis. BMJ 352:i851, 2016
35. Magli A, Moretti E, Tullio A, et al: Hypofractionated simultaneous integrated boost (IMRT-SIB) with pelvic nodal irradiation and concurrent androgen deprivation therapy for high-risk prostate cancer: Results of a prospective phase II trial. Prostate Cancer Prostatic Dis 21:269-276, 2018
36. Vandenbroucke JP: When are observational studies as credible as randomised trials? Lancet 363:1728-1731, 2004

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Treatment-Related Toxicity Using Prostate-Only Versus Prostate and Pelvic Lymph Node Intensity-Modulated Radiation Therapy: A National Population-Based Study

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Student ID Number	LSH1800100	**Title**	Dr
First Name(s)	Matthew		
Surname/Family Name	Parry		
Thesis Title	Use of routinely collected hospital data to explore access to and outcomes from different radiotherapy treatment strategies for locally advanced prostate cancer: national population-based studies.		
Primary Supervisor	Professor Jan van der Meulen		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	International Journal of Radiation Oncology, Biology, Physics		
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SECTION E

Student Signature	M. Parry
Date	8/1/21

Supervisor Signature	J. van der Meulen
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Clinical Investigation

Toxicity of Pelvic Lymph Node Irradiation With Intensity Modulated Radiation Therapy for High-Risk and Locally Advanced Prostate Cancer: A National Population-Based Study Using Patient-Reported Outcomes

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Jan van der Meulen, and Ajay Aggarwal made equal contributions to this study.

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Data-sharing statement: The cancer registry data used for this study are based on information collected and quality assured by Public Health England's National Cancer Registration Service (www.ncras.nhs.uk). Access to the data was facilitated by the Public Health England's Office for Data Release. Hospital Episode Statistics were made available by the NHS Digital (www.digital.nhs.uk), all rights reserved. M.G.P. had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. Data are not available to other researchers because they use existing national data sets.

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Purpose: Little is known about the toxicity of additional pelvic lymph node irradiation in men receiving intensity modulated radiation therapy (IMRT) for prostate cancer. The aim of this study was to compare patient-reported outcomes after IMRT to the prostate only (PO-IMRT) versus the prostate and pelvic lymph nodes (PPLN-IMRT).

Methods and Materials: Patients who received a diagnosis of high-risk or locally advanced prostate cancer in the English National Health Service between April 2014 and September 2016 who were treated with IMRT were mailed a questionnaire at least 18 months after diagnosis. Patient-reported urinary, sexual, bowel, and hormonal functional domains on a scale from 0 to 100, with higher scores indicating better outcomes, and generic health-related quality of life were collected using the Expanded Prostate Cancer Index Composite 26-item version and EQ-5D-5L. We used linear regression to compare PPLN-IMRT versus PO-IMRT with adjustment for patient, tumor, and treatment characteristics.

Results: Of the 7017 men who received a questionnaire, 5468 (77.9%) responded; 4196 (76.7%) had received PO-IMRT and 1272 (23.3%) PPLN-IMRT. Adjusted differences in the Expanded Prostate Cancer Index Composite 26-item version domain scores were smaller than 1 (P always $>.2$), except for sexual function, with men who had PPNL-IMRT reporting a lower mean score (adjusted difference, 2.3; 95% confidence interval, 0.9-3.7; $P = .002$). This did not represent a clinically relevant difference. There was no significant difference in health-related quality of life ($P = .5$).

Conclusions: Additional pelvic lymph node irradiation does not lead to clinically meaningful increases in the toxicity of IMRT for prostate cancer according to patient-reported functional outcomes and health-related quality of life.

Introduction

In the United Kingdom, the National Institute for Health and Care Excellence currently recommends considering pelvic lymph node (PLN) irradiation for patients with a high risk of nodal involvement (Roach score $\geq$15%).[1] However, according to results of the National Prostate Cancer Audit (NPCA), only 18% of men undergoing radiation therapy (RT) between 2010 and 2013 with high-risk or locally advanced prostate cancer had PLN irradiation.[2]

Recently published results from the systemic therapy in advancing or metastatic prostate cancer: evaluation of drug efficacy (STAMPEDE) trial support the routine use of RT in men with nonmetastatic prostate cancer who have positive PLNs, where conformal or intensity modulated RT (IMRT) was used.[3] The 10-year follow-up results of the NRG/Radiation Therapy Oncology Group 9413 trial indicate a benefit of PLN irradiation in terms of progression-free survival when used alongside androgen deprivation therapy (ADT),[4,5] but results of other randomized controlled trials were inconclusive.[6,7] The relevance of all these trials is somewhat limited, given that they were conducted in the pre−dose-escalation era when RT doses did not exceed 64 Gy and IMRT was not used.

The use of PLN irradiation in clinical practice is limited, most likely because of concerns about its worse toxicity compared with prostate-only (PO) RT. However, we recently demonstrated that there is no evidence of an association between additional PLN irradiation and severe gastrointestinal (GI) and genitourinary (GU) toxicity within 3 years of IMRT. Our study included 5468 men diagnosed with prostate cancer between 2010 and 2013 in England and used clinical measures of toxicity derived from linked national cancer registry, RT, and administrative hospital data.[2,8]

To date, studies have not used patient-reported outcome measures (PROMs) to compare groups of patients who received IMRT with and without PLN irradiation. Studies using PROMs are needed because clinical measures based on clinical diagnostic and procedure data do not always fully capture the outcomes that are relevant to patients.[9] We used data collated for the NPCA to compare patient-reported functional outcomes in patients with high-risk or locally advanced prostate cancer who had IMRT to either the PO or the prostate and PLNs (PPLN-IMRT).

Methods and Materials

Patient population

This study used NPCA data derived from English Cancer Registry data,[10] the National Radiotherapy Dataset (RTDS),[11] and Hospital Episode Statistics (HES)[12] to identify men who received a diagnosis of prostate cancer between April 1, 2014 and September 30, 2016 and were treated with radical RT. The International Classification of Diseases 10th Edition code C61 and cancer stage information from the cancer registry data were used to identify men with prostate cancer, and the Office of Population Censuses and Surveys Classification of Interventions and Procedures Version 4 code X671in the RTDS was used to

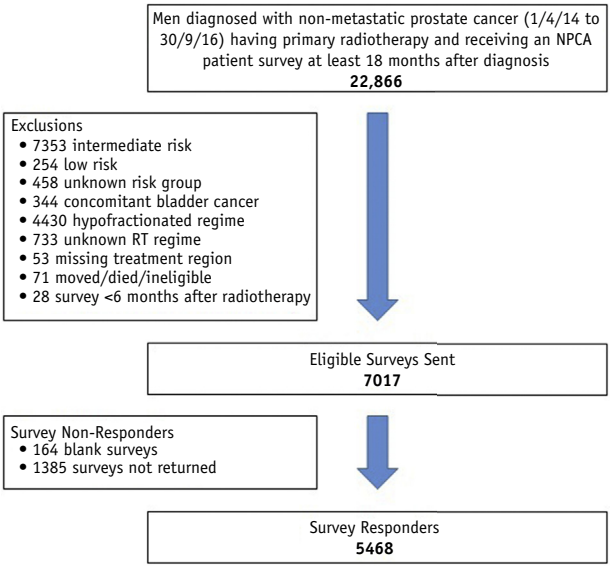

Fig. 1. Flowchart of patient selection.

identify men who had received IMRT[13]; 22,866 men with nonmetastatic prostate cancer who received IMRT were identified in this way (Fig. 1).

Prostate cancer risk was based on TNM stage, Gleason score, and prostate-specific antigen level according to a modified D'Amico risk stratification algorithm developed previously by the NPCA.[8,14] Men were excluded if they had intermediate-risk disease (n = 7353), low-risk disease (n = 254), or unknown prostate cancer risk (n = 458).

The RTDS provided information on RT doses and number of attendances to classify each RT regimen. Men were excluded if they underwent a hypofractionated RT regimen (n = 4430), if they did not have a recognized RT regimen (n = 733), or if the RT treatment region could not be established (n = 53). Finally, men were excluded if they had moved or died (n = 71) or had received RT less than 6 months before completing the survey (n = 28). As a result, 7017 men were eligible for inclusion in the study.

Patient survey

Patient questionnaires were mailed to men eligible for inclusion at least 18 months after diagnosis. Two reminders were sent to nonresponders 4 and 8 weeks after the initial mailing (Appendix E1: NPCA Patient Survey). Median time from diagnosis to RT was 5.4 months (interquartile range [IQR], 4.5-6.9) and 5.7 months (IQR, 4.7-7.8), and median time from RT to survey completion was 16.2 months (IQR, 13.8-22.1) and 15.1 months (IQR, 13.0-19.1) for the PO-IMRT and PPLN-IMRT groups, respectively.

The questionnaire included the Expanded Prostate Cancer Index Composite 26-item version (EPIC-26), a validated instrument to measure functional outcomes in men with prostate cancer in the following 5 domains: urinary incontinence, urinary irritation/obstruction, and sexual, bowel, and hormonal function.[15] Each domain contains between 4 to 7 items. Scores were summarized for each domain on a scale of 0 to 100, with higher scores representing better function. The questionnaire also includes the EuroQol (EQ-5D-5L), which describes generic health-related quality of life (HRQoL) based on 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), with a score expressed on a scale with 0 representing "death" and 1 representing "perfect health."[16] Minimal clinically important differences, which are thresholds for clinically relevant differences, have been previously estimated for each EPIC-26 domain (urinary incontinence, 6-9 point change; urinary irritation/obstruction, 5-7 point change; sexual function, 10-12 point change; bowel function, 4-6 point change; and hormonal function, 4-6 point change)[17] and for the EQ-5D-5L (minimal clinically important difference threshold, 0.08).[18]

Study outcome

Primary outcomes were the 5 EPIC-26 domain scores and the EQ-5D-5L score according to treatment region (PO-IMRT vs PPLN-IMRT). Missing response data for individual questions were handled according to the specific guidelines for EPIC-26. An EPIC-26 domain score was still calculated if at least 80% of the items that comprise a domain summary score were available.[19]

Explanatory variables

The RTDS was used to determine the RT treatment region (PO and PPLN). Given that PPLN-IMRT is usually divided into a PPLN dose and a PO boost dose, it was possible to ascertain only the total PPLN dose and not the isolated dose delivered to the PLNs. HES records were used to determine age, ethnicity, and socioeconomic deprivation according to the Index of Multiple Deprivation,[20] and the number of comorbid conditions was determined according to the Royal College of Surgeons (RCS) Charlson score.[21] T-stage, N-stage, M-stage, Gleason score, and prostate-specific antigen were identified from the cancer registry data. Information on ADT use and number of comorbid conditions was available from the patient survey. Comorbidity data from the patient surveys were used for the primary analysis, and the RCS Charlson score from HES was only used for the comparison between survey responders and nonresponders.

We identified GI and GU procedure codes in HES records of hospital admissions within 1 year before the start of RT as a proxy for baseline GI and GU function. The procedure codes were based on a previously developed coding framework, developed using administrative hospital records, to identify GI and GU toxicity of RT for prostate cancer.[22] PROMs were not collected at the time of diagnosis as part of the NPCA patient survey, but we adjusted

for GI and GU procedures recorded within 1 year before RT instead.

The questionnaire in the second year of the study included 3 questions asking patients to recall urinary, bowel, and sexual function at the time of diagnosis on a 5-point scale ranging from "no problem" to "large problem" so that an assessment of function at the time of diagnosis could be made. Fifty-nine percent and 57% of the included men had available recall results for baseline urinary, bowel, and sexual function, respectively.

Statistical analysis

Multivariable linear regression was used to compare outcomes (EPIC-26 domain and EQ-5D-5L scores) between the PO-IMRT and PPLN-IMRT groups. The comparison was adjusted for patient characteristics (treatment year, age, ethnicity, socioeconomic deprivation status [national quintiles], number of comorbidities [0, 1, or $\geq$2], pretreatment GI and GU procedures, ADT use, and time between RT and completion of survey [6-12, 12-18, and $>$18 months]). A random intercept was modelled for each hospital to represent clustering of outcomes within hospitals. Missing values for adjustment variables (ethnicity) and outcomes were imputed using multiple imputation by chained equations so that we could include all survey responders. Twenty-five data sets were created and Rubin's rules were used to combine the estimates. All analyses were performed using Stata version 14.

Results

Survey response

Of the 7017 men eligible for inclusion in the study, 5468 (77.6%) responded. Responders tended to be older, more frequently of a white ethnic background, from less socially deprived areas, and have fewer comorbidities than nonresponders. There were no differences in response rates between PO-IMRT and PPLN-IMRT groups (Table E1).

Patient population

Of the 5468 responders, 1272 (23.3%) received PLN irradiation (Table 1). There were only small differences in patient characteristics between the PO-IMRT and PPLN-IMRT groups. The median dose per fraction and total dose to the prostate were the same in both groups (2 Gy per fraction and 74 Gy, respectively). Men receiving PPLN-IMRT were more likely to have received ADT (83.4%) than men receiving PO-IMRT (78.6%). There were only small differences between the PO-IMRT and PPLN-IMRT groups in the frequency of men who had undergone GU procedures (21.0% and 22.5%, respectively) or GI procedures (5.4 and 4.8%, respectively) within 1 year before the start of RT.

There were no relevant differences between the PO-IMRT and the PPLN-IMRT groups in recall of bowel and sexual function at the time of diagnosis. Of those who had PO-IMRT, 2.0% and 21.2% rated their bowel and sexual function as a "large problem," respectively, with corresponding percentages for those who had PPLN-IMRT being 1.8% and 19.5%, respectively. However, more men who had PPLN-IMRT rated their urinary function at the time of diagnosis as a "large problem" (16.1%) than men who had PO-IMRT (12.9%).

Outcome measures

Mean EPIC-26 scores were between 85.5 and 86.8 for urinary and bowel function domains. Scores were lower for hormonal function (PPLN-IMRT, 65.3; PO-IMRT, 70.3) and very low for sexual function (PPLN-IMRT, 13.0; PO-IMRT, 14.1) (Table 2).

The PPLN-IMRT group had a lower mean EPIC-26 sexual function score than the PO-IMRT group, but the difference was small (adjusted difference, 2.3; 95% confidence interval, 0.9-3.7) and did not meet the recognized threshold for a clinically relevant difference (Table 2). Differences in the other EPIC-26 domain scores between the treatment groups (urinary incontinence, urinary irritation/obstruction, bowel function, and hormonal function) were small (always $<$1) and not statistically significant. EQ-5D-5L scores were not statistically different between groups either (both 0.84), where a clinically meaningful difference corresponds to a difference of at least 0.08.[18]

Discussion

There were no clinically relevant differences in function or generic HRQoL between men who were treated with either PO-IMRT or PPLN-IMRT, according to self-reported outcomes at least 18 months after diagnosis of high-risk or locally advanced prostate cancer. This is the first study to use PROMs to compare PO and PPLN irradiation using modern dose-escalation techniques showing that additional irradiation of the PLNs does not increase long-term toxicity.

Comparison with other studies

Three relatively small studies have previously used PROMs to assess the toxicity of additional PLN irradiation. Two of these studies used 3-dimensional conformal RT and did not find clinically relevant differences in HRQoL between 12 and 24 months after the end of RT. The first was a randomized controlled trial of 444 patients published in 2007, and the second was a cohort study of 120 patients published in 2011.[7,23] The third study was a cohort study of 120 patients, published in 2014, which used IMRT to treat the PLNs and 3-dimensional

Table 1 Patient characteristics by radiation therapy group (PO-IMRT or PPLN-IMRT)

	PO-IMRT		PPLN-IMRT		All	
Characteristics	n	%	n	%	n	%
	4196	76.7	1272	23.3	5468	100
Treatment year						
2014	723	17.2	274	21.5	997	18.2
2015	1871	44.6	421	33.1	2292	41.9
2016	1602	38.2	577	45.4	2179	39.9
Age (y)						
≤60	156	3.7	102	8.0	258	4.7
61-70	1428	34.0	501	39.4	1929	35.3
71-80	2340	55.8	618	48.6	2958	54.1
>80	272	6.5	51	4.0	323	5.9
Ethnicity						
White	3782	97	1107	94.0	4889	96.3
Mixed	9	0.2	4	0.3	13	0.3
Asian	40	1.0	20	1.7	60	1.2
Black	39	1.0	36	3.1	75	1.5
Other	29	0.7	11	0.9	40	0.8
Missing	297		94		391	
Socioeconomic deprivation quintiles, national distribution)						
1 (least)	953	22.7	326	25.6	1279	23.4
2	1095	26.1	309	24.3	1404	25.7
3	942	22.4	274	21.5	1216	22.2
4	711	16.9	214	16.8	925	16.9
5 (worst)	495	11.8	149	11.7	644	11.8
No. of comorbidities (RCS Charlson score)						
0	825	19.7	272	21.4	1097	20.1
1	1273	30.3	420	33.0	1693	31.0
≥2	2098	50.0	580	45.6	2678	49.0
Urinary procedure 1 y before start of radiation therapy						
No	3315	79.0	986	77.5	4301	78.7
Yes	881	21.0	286	22.5	1167	21.3
Bowel procedure 1 y before start of radiation therapy						
No	3968	94.6	1211	95.2	5179	94.7
Yes	228	5.4	61	4.8	289	5.3
Androgen deprivation therapy						
No	896	21.4	211	16.6	1107	20.2
Yes	3300	78.6	1061	83.4	4361	79.8

Abbreviations: IMRT = intensity modulated radiation therapy; PO = prostate only; PPLN = prostate and pelvic lymph nodes; RCS = Royal College of Surgeons.

conformal RT to treat the prostate.[24] This study found that urinary and bowel function were worse for the PPLN group at 3 months after RT but function was comparable at 12 months, representing a difference in acute toxicity that resolved over time.

Results from studies using clinician-reported outcome measures are in line with the studies using PROMs. One small cohort study of 277 patients, using IMRT to treat the prostate and a 4-field technique for the PLNs, showed that there were no longer-term differences between those who did and did not have PLN irradiation.[25] Similarly, a study that we carried out recently, using linked national data sets, to compare 3065 men who had PO-IMRT and 780 who had PPLN-IMRT found no evidence of differences in GI or GU toxicity 3 years after diagnosis.[2]

Table 2 Adjusted differences in patient-reported outcomes after IMRT for high-risk or locally advanced prostate cancer

	PO-IMRT	PPLN-IMRT	Adjusted difference in means*	95% CI	*P* values
No. of patients (%)	4196 (76.7)	1272 (23.3)			
EPIC-26 domains					
Urinary incontinence					
Mean (SD)	86.2 (19.0)	86.8 (19.5)	−0.2	−1.2 to 0.8	.7
Missing	575	130			
Urinary irritation/ obstruction					
Mean (SD)	86.3 (14.8)	86.8 (14.5)	0.6	−0.4 to 1.6	.2
Missing	862	212			
Sexual function					
Mean (SD)	14.1 (18.1)	13.0 (15.6)	−2.3	−3.7 to −0.9	.002
Missing	334	107			
Bowel function					
Mean (SD)	85.6 (18.4)	85.5 (18.6)	0.2	−1.1 to 1.5	.7
Missing	617	147			
Hormonal function					
Mean (SD)	66.1 (23.3)	64.2 (22.9)	−0.3	−2.1 to 1.6	.8
Missing	503	118			
Health-related quality of life					
EQ-5D-5L					
Mean (SD)	0.84 (0.19)	0.84 (0.18)	−0.04	−0.01 to 0.01	.5
Missing	121	24			

Abbreviations: CI = confidence interval; EPIC = Expanded Prostate Cancer Index Composite; EQ-5D-5L = EuroQol; IMRT = intensity modulated radiation therapy; PO = prostate only; PPLN = prostate and pelvic lymph nodes; SD = standard deviation.

* Adjusted for treatment year, age, ethnicity, socioeconomic deprivation (quintiles of national distribution), number of comorbidities (0, 1, ≥2), pretreatment gastrointestinal and genitourinary procedures, androgen deprivation therapy, and time between radiation therapy and completion of survey.

Strengths and limitations

The strengths of the current study include the relatively large number of patients (n = 5468), the high response rate to the survey (78%), and the use of validated instruments to collect PROMs at a specified time after diagnosis. It is the largest study to date comparing functional outcomes and generic HRQoL in patients who had PO-IMRT and those who had PPLN-IMRT. A further strength is that we used recent national data sets, which ensures that our results are fully representative of modern-day clinical practice.

The main limitation of the study was the lack of baseline PROMs (EPIC-26 and EQ-5D-5L scores) at the time of diagnosis, but the regression analyses were still adjusted for important patient characteristics and prior GI and GU procedures. Therefore, the impact of including baseline PROMs in the models is likely to be small given that they would only be supplying additional adjustment beyond what is already captured. We also included 3 questions in the patient survey asking patients to recall their baseline urinary, bowel, and sexual function. Our results show that more men who had PPLN-IMRT rated their urinary function at the time of diagnosis as a "large problem" compared with men who had PO-IMRT. If there was residual confounding present due to this difference in baseline urinary function, we would expect the observed results to indicate worse urinary function after PPLN-IMRT compared with PO-IMRT. Given that this is not the case, residual confounding is likely to be small and further supports the interpretation of our findings as indicating that additional PLN irradiation does not increase long-term toxicity compared with PO-IMRT. In addition, for the 57% of the study cohort for whom recalled baseline function results were available, a sensitivity analysis was performed adjusting for these additional variables, and results were the same as the overall study results.

Although the response rate was high for a national patient survey, we need to consider the potential impact of selective nonresponse. It is important to note that the response rates did not vary between the PO-IMRT and PPLN-IMRT groups. Furthermore, the differences we report were adjusted for patient characteristics that have been shown to be associated with survey response (age and comorbidity), which further reduces the impact of selective nonresponse on our results.

Clinical implications

The life expectancy of men with prostate cancer is increasing; as a result, men are living longer with their

disease and with treatment-related side effects.[26,27] PROMs are therefore providing essential information for evaluation of the benefits and harms of radical prostate cancer treatment.[28,29]

We did not find evidence that PPLN-IMRT is associated with clinically relevant differences in longer-term functional outcomes or HRQoL. This suggests that PPLN-IMRT should be considered in patients with high-risk or locally advanced prostate cancer, especially given emerging evidence that relapse patterns are often nodal-centric.[30] In addition, with the advent of molecular imaging, men can be more appropriately assessed with respect to lymph node involvement. This will improve decision making with regard to the inclusion of PLNs within the radiation field as part of primary treatment or when used in the salvage setting.

Conclusions

There are no clinically relevant differences in functional outcomes or HRQoL in men with high-risk or locally advanced prostate cancer who undergo PO-IMRT or PPLN-IMRT.

References

1. National Institute for Health and Care Excellence (NICE). Prostate Cancer: Diagnosis and Treatment. Available at: http://www.nice.org.uk/guidance/cg175. Accessed January 8, 2018.
2. Parry MG, Sujenthiran A, Cowling TE, et al. Treatment-related toxicity using prostate only vs prostate and pelvic lymph node intensity modulated radiation therapy: A national population-based study. *J Clin Oncol* 2019;27:1828-1835.
3. James ND, Spears MR, Clarke NW, et al. Failure-free survival and radiotherapy in patients with newly diagnosed nonmetastatic prostate cancer: Data from patients in the control arm of the STAMPEDE trial. *JAMA Oncol* 2016;2:348-357.
4. Lawton CA, DeSilvio M, Roach M 3rd, et al. An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: Updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. *Int J Radiat Oncol Biol Phys* 2007;69:646-655.
5. Roach M, Moughan J, Lawton CAF, et al. Sequence of hormonal therapy and radiotherapy field size in unfavourable, localised prostate cancer (NRG/RTOG 9413): Long-term results of a randomised, phase 3 trial. *Lancet Oncol* 2018;19:1504-1515.
6. Asbell SO, Krall JM, Pilepich MV, et al. Elective pelvic irradiation in stage A2, B carcinoma of the prostate: Analysis of RTOG 77-06. *Int J Radiat Oncol Biol Phys* 1988;15:1307-1316.
7. Pommier P, Chabaud S, Lagrange JL, et al. Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Preliminary results of GETUG-01. *J Clin Oncol* 2007;25:5366-5373.
8. National Prostate Cancer Audit. Annual Report 2018: Results of the NPCA prospective audit in England and Wales for men diagnosed from 1 April 2016 - 31 March 2017. Available at: https://www.npca.org.uk/reports/npca-annual-report-2018/. Accessed May 14, 2019.
9. Di Maio M, Basch E, Bryce J, Perrone F. Patient-reported outcomes in the evaluation of toxicity of anticancer treatments. *Nat Rev Clin Oncol* 2016;13:319-325.
10. National Cancer Intelligence Network. National Cancer Data Repository. Available at: http://www.ncin.org.uk/collecting_and_using_data/national_cancer_data_repository/. Accessed December 11, 2016.
11. National Cancer Registration and Analysis Service. National Radiotherapy Dataset (RTDS). Available at: http://www.ncin.org.uk/collecting_and_using_data/rtds. Accessed December 11, 2017.
12. National Health Service. Hospital Episode Statistics. Available at: http://www.hesonline.nhs.uk. Accessed January 15, 2017.
13. National Health Service. OPCS-4 Classification of Interventions and Procedures. Available at: http://www.digital.nhs.uk/article/1117/Clinical-Classifications. Accessed January 8, 2018.
14. Parry MG, Sujenthiran A, Cowling TE, et al. Imputation of missing prostate cancer stage in English cancer registry data based on clinical assumptions. *Cancer Epidemiol* 2019;58:44-51.
15. Szymanski KM, Wei JT, Dunn RL, Sanda MG. Development and validation of an abbreviated version of the expanded prostate cancer index composite instrument for measuring health-related quality of life among prostate cancer survivors. *Urology* 2010;76:1245-1250.
16. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20:1727-1736.
17. Skolarus TA, Dunn RL, Sanda MG, et al. Minimally important difference for the Expanded Prostate Cancer Index Composite Short Form. *Urology* 2015;85:101-105.
18. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health Qual Life Outcomes* 2007;5:70.
19. University of Michigan. Scoring instructions for the Expanded Prostate Cancer Index Composite Short Form (EPIC-26) (2002). Available at: https://medicine.umich.edu/sites/default/files/content/downloads/Scoring%20Instructions%20for%20the%20EPIC%2026.pdf. Accessed May 14, 2019.
20. Noble M, McLennan D, Wilkinson K, Whitworth A, Dibben C, Barnes H. The English Indices of Deprivation 2007. Available at: http://geoconvert.mimas.ac.uk/help/imd-2007-manual.pdf. Accessed September 28, 2017.
21. Armitage JN, van der Meulen JH. Identifying co-morbidity in surgical patients using administrative data with the Royal College of Surgeons Charlson Score. *Br J Surg* 2010;97:772-781.
22. Sujenthiran A, Nossiter J, Charman SC, et al. National population-based study comparing treatment-related toxicity in men who received intensity modulated versus 3-dimensional conformal radical radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2017;99:1253-1260.
23. Pinkawa M, Piroth MD, Holy R, et al. Quality of life after whole pelvic versus prostate-only external beam radiotherapy for prostate cancer: A matched-pair comparison. *Int J Radiat Oncol Biol Phys* 2011;81:23-28.
24. Lilleby W, Stensvold A, Dahl AA. Adding intensity-modulated radiotherapy to the pelvis does not worsen the adverse effect profiles compared to limited field radiotherapy in men with prostate cancer at 12-month follow-up. *Acta Oncol* 2014;53:1380-1389.
25. Aizer AA, Yu JB, McKeon AM, Decker RH, Colberg JW, Peschel RE. Whole pelvic radiotherapy versus prostate only radiotherapy in the management of locally advanced or aggressive prostate adenocarcinoma. *Int J Radiat Oncol Biol Phys* 2009;75:1344-1349.
26. Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med* 2008;358:1250-1261.
27. Miller DC, Sanda MG, Dunn RL, et al. Long-term outcomes among localized prostate cancer survivors: Health-related quality-of-life changes after radical prostatectomy, external radiation, and brachytherapy. *J Clin Oncol* 2005;23:2772-2780.
28. Chou R, Croswell JM, Dana T, et al. Screening for prostate cancer: A review of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2011;155:762-771.

29. Calvert M, Blazeby J, Altman DG, Revicki DA, Moher D, Brundage MD. Reporting of patient-reported outcomes in randomized trials: The CONSORT PRO extension. *JAMA* 2013;309:814-822.

30. De Bruycker A, De Bleser E, Decaestecker K, et al. Nodal oligorecurrent prostate cancer: Anatomic pattern of possible treatment failure in relation to elective surgical and radiotherapy treatment templates. *Eur Urol* 2018;75:826-833.

7 BRACHYTHERAPY BOOST

7.1 Research Paper 6

Title: Impact of high-dose rate and low-dose rate brachytherapy boost on toxicity, functional and cancer outcomes in patients receiving external beam radiation therapy for prostate cancer: a national population-based study.

The online PDF version can be accessed at:

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Student ID Number	LSH1800100	**Title**	Dr
First Name(s)	Matthew		
Surname/Family Name	Parry		
Thesis Title	Use of routinely collected hospital data to explore access to and outcomes from different radiotherapy treatment strategies for locally advanced prostate cancer: national population-based studies.		
Primary Supervisor	Professor Jan van der Meulen		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

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Where was the work published?	International Journal of Radiation Oncology, Biology, Physics		
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Clinical Investigation

Impact of High-Dose-Rate and Low-Dose-Rate Brachytherapy Boost on Toxicity, Functional and Cancer Outcomes in Patients Receiving External Beam Radiation Therapy for Prostate Cancer: A National Population-Based Study

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Jan van der Meulen and Ajay Aggarwal are joint senior authors and made equal contributions to this study and manuscript.

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The cancer registry data used for this study are based on information collected and quality assured by Public Health England's National Cancer Registration Service (www.ncras.nhs.uk). Access to the data was facilitated by the Public Health England's Office for Data Release. Hospital Episode Statistics were made available by the NHS Digital (www.digital.nhs.uk); all rights reserved. MGP had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. Data are not available to other researchers as it uses existing national data sets.

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Purpose: External beam radiation therapy (EBRT) with brachytherapy boost reduces cancer recurrence in patients with prostate cancer compared with EBRT monotherapy. However, randomized controlled trials or large-scale observational studies have not compared brachytherapy boost types directly.

Methods and Materials: This observational cohort study used linked national cancer registry data, radiation therapy data, administrative hospital data, and mortality records of 54,642 patients with intermediate-risk, high-risk, and locally advanced prostate cancer in England. The records of 11,676 patients were also linked to results from a national patient survey collected at least 18 months after diagnosis. Competing risk regression analyses were used to compare gastrointestinal (GI) toxicity, genitourinary (GU) toxicity, skeletal-related events (SRE), and prostate cancer−specific mortality (PCSM) at 5 years with adjustment for patient and tumor characteristics. Linear regression was used to compare Expanded Prostate Cancer Index Composite 26-item version domain scores (scale, 0-100, with higher scores indicating better function).

Results: Five-year GI toxicity was significantly increased after low-dose-rate brachytherapy boost (LDR-BB) (32.3%) compared with high-dose-rate brachytherapy boost (HDR-BB) (16.7%) or EBRT monotherapy (18.7%). Five-year GU toxicity was significantly increased after both LDR-BB (15.8%) and HDR-BB (16.6%), compared with EBRT monotherapy (10.4%). These toxicity patterns were matched by the mean patient-reported bowel function scores (LDR-BB, 77.3; HDR-BB, 85.8; EBRT monotherapy, 84.4) and the mean patient-reported urinary obstruction/irritation function scores (LDR-BB, 72.2; HDR-BB, 78.9; EBRT monotherapy, 83.8). Five-year incidences of SREs and PCSM were significantly lower after HDR-BB (2.4% and 2.7%, respectively) compared with EBRT monotherapy (2.8% and 3.5%, respectively).

Conclusions: Compared with EBRT monotherapy, LDR-BB has worse GI and GU toxicity and HDR-BB has worse GU toxicity. HDR-BB has a lower incidence of SREs and PCSM than EBRT monotherapy.

Introduction

Advances in radiation therapy planning and treatment have enabled higher radiation doses to be delivered to the prostate.[1] These higher doses can also be achieved by using a brachytherapy boost (BB) in addition to external beam radiation therapy (EBRT). Three randomized controlled trials (RCT) have compared EBRT only (hereafter referred to as EBRT monotherapy irrespective of concomitant hormone therapy) to EBRT with a BB, and all showed a benefit in terms of biochemical cancer control.[2-8]

Observational data suggests lower prostate cancer−specific mortality (PCSM) after EBRT with either a high-dose-rate brachytherapy boost (HDR-BB) or low-dose-rate brachytherapy boost (LDR-BB) compared with EBRT monotherapy.[9-15] However, no RCT or large-scale observational study has compared brachytherapy boost types directly. The only current evidence is a retrospective single-center study comparing HDR-BB to LDR-BB delivered across 2 different periods.[16] LDR-BB had superior biochemical progression-free survival compared with HDR-BB but worse gastrointestinal (GI) and genitourinary (GU) toxicity. There is consistent evidence suggesting that LDR-BB has worse GI and GU toxicity compared with EBRT monotherapy,[7,8] whereas HDR-BB has been shown to have a better GI toxicity profile compared with EBRT monotherapy.[3,17-19]

HDR-BB and LDR-BB have not been compared directly with respect to toxicity, functional outcomes or cancer outcomes. We therefore used electronic health care data from the National Prostate Cancer Audit, and results from its national patient survey, to perform a study of 54,650 prostate cancer patients treated in England comparing toxicity, functional outcomes, skeletal-related events (SRE) and PCSM after HDR-BB, LDR-BB, or EBRT monotherapy.[20]

Methods and Materials

Patient population

This study used English Cancer Registry data,[21] the National Radiotherapy Dataset, (RTDS),[22] and Hospital Episode Statistics (HES)[23] linked at the patient level to follow up men with prostate cancer who were treated with radical radiation therapy between January 1, 2010, and December 31, 2016. Follow-up was available until December 31, 2018. The International Classification of Diseases, 10th Edition (ICD-10)[24] code C61 in the cancer registry data was used to identify men with prostate cancer.

A total of 59,381 men who received radical radiation therapy for nonmetastatic intermediate-risk, high-risk, or locally advanced prostate cancer were identified using the

Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, 4th Revision (OPCS-4) code X671 in the RTDS.[25] The cohort was stratified according to a modified D'Amico risk stratification algorithm developed previously by the National Prostate Cancer Audit, which takes account of the lack of baseline prostate-specific antigen data before 2014 and the inability to further subdivide T stage beyond T1-4 (ie, T2a, T2b, or T2c).[26] This stratification system assigns "intermediate-risk" to men with T2 and Gleason score of 7 and "locally advanced" to men with T3, T4, or N1. Men with a Gleason score of 8 or higher (high-risk) were also included in this latter group in the same way as the National Institute for Health and Care Excellence guidelines and is termed "high-risk or locally advanced" throughout.[27] Exclusions were made for men who could not be assigned to a radiation therapy (n = 168) or brachytherapy center (n = 35), those with a concomitant diagnosis of bladder cancer (n = 1686), or those where the radiation therapy regimen was unknown (n = 2848). Men who received a BB who could not be assigned to either HDR-BB or LDR-BB were also excluded (n = 5). The final cohort included 54,642 men who received EBRT for prostate cancer between 2010 and 2016 for whom at least 2 years of follow-up was available (Fig. 1).

National patient survey

Patient records for the final cohort were also linked to a national patient-reported outcome survey developed and conducted by the National Prostate Cancer Audit, which included the Expanded Prostate Cancer Index Composite 26-item version (EPIC-26), a validated instrument to measure health-related quality of life related to prostate cancer (Supplementary Material - NPCA Patient Survey).[28] All men diagnosed with prostate cancer between April 1, 2014 and September 30, 2016 who received radical treatment were included and the survey was mailed at least 18 months after diagnosis. Two reminders were sent to nonresponders at 4 and 8 weeks. The survey was sent out to 15,041 eligible men who had received treatment at least 6 months before the survey, 11,676 of whom responded (77.6%).

GI and GU Toxicity

We used previously validated indicators to identify men who experienced urinary or bowel-related toxicity that required a diagnostic or therapeutic procedure after radiation therapy.[29] GI or GU toxicity was defined as the presence of both an ICD-10 diagnostic code[24] and an OPCS-4 procedure code[25] in a patient's HES record which were related to complications after radiation therapy (Tables E1 and E2). This is comparable to toxicity of at least grade 2 according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (moderate severity requiring local or noninvasive interventions).[30]

We also developed indicators representing GI and GU toxicity of at least grade 3 (severe or medically significant severity requiring hospitalization or prolongation of hospitalization).[30] A complication was deemed to be at least grade 3 if the procedure performed included a therapeutic intervention (Tables E1 and E2).

Functional outcomes

We used 3 EPIC-26 domains (urinary incontinence, urinary obstruction/irritation, and bowel function), each summarized on a scale of 0 to 100, with higher scores representing better function.[28] Missing response data to individual items were handled according to specific EPIC-26 guidelines.[31]

Skeletal-related events

The occurrence of SREs was used as a measure of treatment effectiveness. SREs were defined as either a pathological fracture, spinal cord compression, bone surgery, or palliative radiation therapy based on ICD-10 diagnostic and OPCS-4 procedure codes in HES, and radiation therapy codes in the RTDS, according to the specific definition.[32]

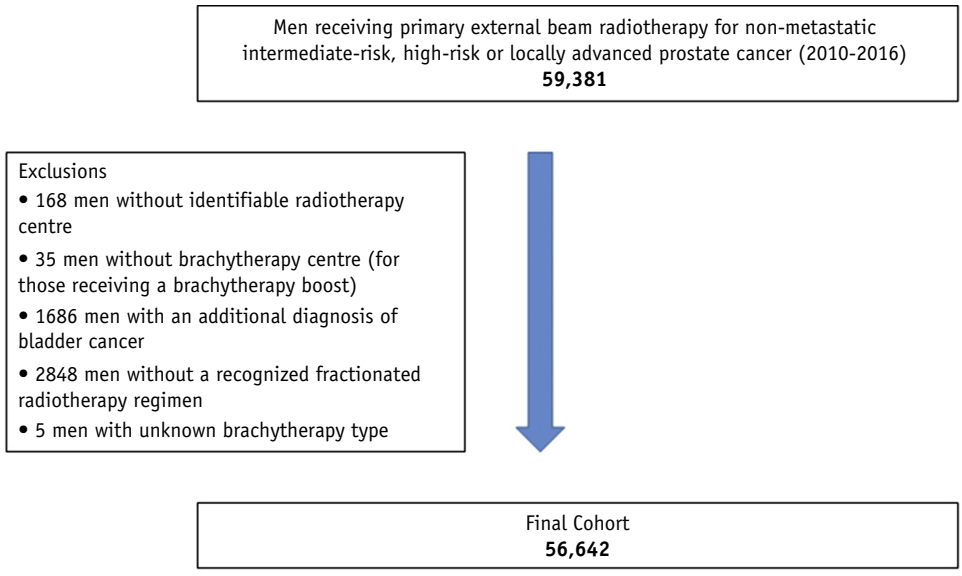
Mortality

The Office for National Statistics provided dates of death. PCSM was defined as any death in which prostate cancer was identified on the death certificate as part of the sequence leading to death.

Explanatory and control variables

The RTDS provided information on radiation therapy and brachytherapy doses. Patients were allocated to EBRT monotherapy or BB groups based on recognized EBRT regimens and brachytherapy doses (Fig. 1). When brachytherapy dose information was missing from the RTDS (46.6%), the brachytherapy type was derived from the type usually given at each hospital (based on the results from the National Prostate Cancer Audit organizational survey) and from within-center validation with the lead clinicians. If the brachytherapy hospital was missing from the RTDS, HES records were used for this where brachytherapy episodes were identified by specific OPCS-4 code combinations (M706 + X653 + Y363, M706 + X653, M712 + X653). There were a total of 53, 12, and 8 hospitals which provided EBRT monotherapy, HDR-BB, and LDR-BB, respectively.

Data items in the HES records in the year before diagnosis were used to determine the number of comorbidities according to the Royal College of Surgeons Charlson score.[33] Socioeconomic deprivation status was



Included fractionated regimes:

EBRT only cohort RT regimen (Gy/Fractions)	BB cohort RT regimen (Gy/Fractions)	BB cohort BT regimen (Gy)
72-79/35-49	36-39/15	< 30 (HDR)
72/32	43-47/22-25	≥ 100 (LDL)
70/35	50/28	
69/37		
50-60/16,19-20 (hypofractionated)		

Fig. 1. Flowchart of patients included in the study.

determined for patients from the English 2015 Index of Multiple Deprivation.[34] T-stage, N-stage, M-stage, and Gleason grade were identified from the cancer registry data. Previous GI and GU procedures were estimated based on the presence of a GI or GU procedure code within the HES record up to a year before diagnosis.[29]

Statistical analysis

We calculated the cumulative incidence of GI and GU toxicity, SREs, and PCSM from the start of radiation therapy until the end of follow-up for a maximum of 5 years. We considered death from any cause as a competing event when analyzing toxicity and SREs, and death from other causes when analyzing PCSM. Fine and Gray competing risk regression analysis was used to estimate subdistribution hazard ratios (sHR) with 95% confidence intervals (CI) to compare incidence rates.[35]

Linear regression analysis was used to estimate differences in EPIC-26 function scores between the treatment groups, where negative differences represent poorer outcomes relative to the reference group. Adjusted differences in EPIC-26 domain scores were interpreted as "clinically important" based on previously reported minimal clinically important differences of 6, 5, and 4 points for the EPIC-26 domains urinary incontinence, urinary irritation/obstruction, and bowel function, respectively.[36]

All regression analyses included the patient and tumor characteristics outlined in Table 1. Age was included as a linear and a quadratic term. Time between the start of radiation therapy and the patient survey (6-12, 12-18, and >18 mo) was also included in the linear regression analyses of EPIC-26 scores. Models were adjusted for clustering of outcomes within hospitals using robust standard errors at the hospital level. Wald tests were used to calculate *P* values. We also assessed the distribution of residuals to check model specification.

Post hoc pairwise tests were carried out with a Bonferroni correction for multiple comparisons when a statistically significant overall difference existed at the 5% level between the 3 treatment groups.[37]

Table 1 Patient, tumor, and treatment characterisitcs of patients who received EBRT monotherapy, HDR-BB, or LDR-BB

	EBRT monotherapy		HDR-BB		LDR-BB		Total	
	N	%	N	%	N	%	N	%
All patients	51,547		2765		330		54,642	
Follow-up, mo*	57.5	40.7-77.5	55.5	39.8-74.7	56.9	38.1-79.6	57.5	40.5-77.3
Treatment year								
2010	3981	7.7	201	7.3	35	10.6	4217	7.7
2011	5272	10.2	242	8.8	35	10.6	5549	10.2
2012	6751	13.1	330	11.9	37	11.2	7118	13.0
2013	7655	14.9	427	15.4	43	13.0	8125	14.9
2014	9330	18.1	513	18.6	47	14.2	9890	18.1
2015	9007	17.5	542	19.6	63	19.1	9612	17.6
2016	9551	18.5	510	18.4	70	21.2	10,131	18.5
Age group, y								
<60	2816	5.5	349	12.6	56	17.0	3221	5.9
60-70	17,975	34.9	1335	48.3	155	47.0	19,465	35.6
70-80	28,067	54.4	1058	38.3	115	34.8	29,240	53.5
>80	2689	5.2	23	0.8	4	1.2	2716	5.0
No. of comorbidities (RCS Charlson score)								
0	41,928	81.3	2411	87.2	277	83.9	44,616	81.7
1	7144	13.9	293	10.6	45	13.6	7482	13.7
≥2	2,475	4.8	61	2.2	8	2.4	2,544	4.7
Deprivation status (national quintiles)								
1 (most affluent)	11,958	23.2	757	27.4	150	45.5	12,865	23.5
2	12,920	25.1	765	27.7	73	22.1	13,758	25.2
3	11,004	21.3	600	21.7	48	14.5	11,652	21.3
4	8620	16.7	419	15.2	41	12.4	9080	16.6
5 (most deprived)	7045	13.7	224	8.1	18	5.5	7287	13.3
Gleason grade								
6	4440	9.4	167	6.5	32	10.2	4639	9.2
7 (3 + 4)	14,833	31.3	643	24.9	147	46.7	15,623	31.1
7 (4 + 3)	9890	20.9	657	25.5	69	21.9	10,616	21.1
8	8076	17.0	521	20.2	27	8.6	8624	17.1
9	10,165	21.4	592	22.9	40	12.7	10,797	21.5
Missing	4143		185		15		4343	
T stage								
1	6725	13.6	293	11.0	33	10.4	7051	13.5
2	21,588	43.8	943	35.5	181	57.1	22,712	43.5
3	20,077	40.7	1389	52.2	103	32.5	21,569	41.3
4	896	1.8	35	1.3	0	0	931	1.8
Missing	2261		105		13		2379	
N stage								
0	39,297	93.8	2116	94.8	233	96.3	41,646	93.8
1	2615	6.2	117	5.2	9	3.7	2741	6.2
Missing	9635		532		88		10,255	
Gastrointestinal procedure 1 year before radiation therapy								
0	49,612	96.2	2677	96.8	319	96.7	52,608	96.3
1	1935	3.8	88	3.2	11	3.3	2034	3.7
Genitourinary procedure 1 year before radiation therapy								
0	48,394	93.9	2650	95.8	321	97.3	51,365	94.0
1	3153	6.1	115	4.2	9	2.7	3277	6.0
Radiation therapy type								
3D conformal	17,079	33.1	1260	45.6	147	44.5	18,486	33.8
IMRT	34,468	66.9	1505	54.4	183	55.5	36,156	66.2
Treatment region								
Prostate only	41,786	87.2	2109	84.6	278	90.3	44,173	87.1

(*continued on next page*)

Table 1 (*continued*)

	EBRT monotherapy		HDR-BB		LDR-BB		Total	
	N	%	N	%	N	%	N	%
Prostate and pelvic lymph nodes	6142	12.8	383	15.4	30	9.7	6555	12.9
Missing	3619		273		22		3914	

Abbreviations: 3D = 3-dimensional; EBRT = external beam radiation therapy; HDR-BB = high-dose-rate brachytherapy boost; IMRT = intensity-modulated radiation therapy; LDR-BB = low-dose-rate brachytherapy boost; RCS = Royal College of Surgeons.
* Results reported as median and interquartile range.

Missing data were imputed using multiple imputation by chained equations.[38] Ten imputed data sets were created, and Rubin's rules used to combine study estimates. Individual EPIC-26 items were imputed using the responses to other items within each EPIC-26 domain score before linear regression so that all survey responders were included.

Results

Patient population

Of the 54,642 men who received EBRT between 2010 and 2016, 2765 (5.1%) received HDR-BB, and 330 (0.6%) received LDR-BB (Table 1) with a median follow-up of 4.5, 4.4, and 4.6 years, respectively. The median age was 71 years (interquartile range, 66-75 y), 10,026 (18.4%) had at least one comorbidity, and 32,529 (59.5%) had high-risk or locally advanced disease. 43.1% had T-stage 3/4, 6.2% had N-stage 1, and 38.6% had a Gleason grade of 8 or higher.

Of the 51,547 men who received EBRT monotherapy, 39,591 (76.8%) had a standard regimen (median total dose, 74 Gy in 37 fractions), with the remaining 11,956 (23.2%) having a hypofractionated regimen (median dose, 60 Gy in 20 fractions). Of the 2765 men in the HDR-BB group, 1225 (44.3%) received 46 Gy in 23 fractions as their EBRT dose and 1197 (43.3%) received a hypofractionated regimen of 37.5 Gy in 15 fractions. The majority of men in the HDR-BB group (82.1%) received a brachytherapy dose of 15 Gy in 1 fraction. Of the 330 men in the LDR-BB group, 133 (40.3%) received 44 Gy in 22 fractions as their EBRT dose, 129 (39.1%) received 45 Gy in 25 fractions, 29 (8.8%) received 50.4 Gy in 28 fractions, and 23 (7.0%) received 46 Gy in 23 fractions. The majority of men in the LDR-BB group (92.1%) received a brachytherapy dose of 110 Gy in 1 fraction.

Both the LDR-BB and HDR-BB groups were more likely to be younger, to have no comorbidities, and to come from more affluent areas than the EBRT monotherapy group (all $P < .05$). The LDR-BB group was also more likely to come from a more affluent area than the HDR-BB group. However, the HDR-BB group had the most advanced cancers (53.5% T3/4 and 43.1% Gleason grade of 8 or higher), whereas the LDR-BB group had the least advanced cancers (32.5% T3/4 and 21.1% Gleason grade of 8 or higher).

GI toxicity

Table 2 and Figure 2 show that the 5-year cumulative incidence of GI toxicity of at least grade 2 was different between the treatment groups ($P < .001$). The LDR-BB group had the highest cumulative incidence (32.3%; 95% CI, 26.9-37.2), followed by the EBRT monotherapy group (18.7%; 95% CI, 18.4-19.1) and the HDR-BB group (16.7%; 95% CI, 15.2-18.2). Post hoc pairwise tests confirmed that the cumulative incidence was statistically significantly lower in men receiving HDR-BB (sHR, 0.48; 95% CI, 0.34-0.70) or EBRT monotherapy (sHR, 0.56; 95% CI, 0.43-0.73) than in men who received LDR-BB, without showing a statistically significant difference between EBRT monotherapy and HDR-BB.

GU toxicity

Table 2 and Figure 2 show that the 5-year cumulative incidence of GU toxicity of at least grade 2 was different between the treatment groups ($P < .001$). HDR-BB (16.6%; 95% CI, 15.1-18.2) and LDR-BB groups (15.8%; 95% CI, 11.9-20.2) had higher cumulative incidences than the EBRT monotherapy group (10.4%; 95% CI, 10.1-10.7). Post hoc pairwise tests confirmed that the cumulative incidence was statistically significantly higher in the HDR-BB (sHR, 1.91; 95% CI, 1.33-2.75) and the LDR-BB groups (sHR, 1.94; 95% CI, 1.02-3.70) than in the EBRT monotherapy group, without showing a statistically significant difference between the brachytherapy boost groups.

Severe toxicity

There was a lower cumulative incidence of GI and GU toxicity of at least grade 3, but the pattern of difference between the treatment groups remained the same (EBRT monotherapy: 3.2% and 4.6%; HDR-BB: 1.8% and 9.0%; LDR-BB: 5.1% and 11.1%, respectively). One specific difference, however, was that GI toxicity of at least grade 3 was significantly lower after HDR-BB compared with EBRT monotherapy (Table E3).

Table 2 Gastrointestinal and genitourinary toxicity, skeletal-related events, and prostate-cancer specific mortality in patients who received EBRT monotherapy, HDR-BB, or LDR-BB

Outcome measure	5-year cumulative incidence, %	95% CI	sHR (95% CI)	*P* value*
Gastrointestinal toxicity				
EBRT	18.7	18.4-19.1	0.56 (0.43-0.73)	<.001
HDR-BB	16.7	15.2-18.2	0.48 (0.34-0.70)	
LDR-BB	32.2	26.9-37.7	1	
Genitourinary toxicity				
EBRT	10.4	10.1-10.7	1	<.001
HDR-BB	16.6	15.1-18.2	1.91 (1.33-2.75)	
LDR-BB	15.8	11.9-20.2	1.94 (1.02-3.70)	
Skeletal-related event				
EBRT	2.8	2.6-3.0	1	.041
HDR-BB	2.4	1.8-3.1	0.72 (0.54-0.97)	
LDR-BB	2.7	1.2-5.4	1.32 (0.73-2.38)	
Prostate cancer-specific mortality				
EBRT	3.5	3.3-3.6	1	.020
HDR-BB	2.7	2.0-3.5	0.75 (0.60-0.94)	
LDR-BB	2.7	1.0-5.9	1.44 (0.69-3.04)	

Abbreviations: CI = confidence interval; EBRT = external beam radiation therapy; HDR-BB = high-dose-rate brachytherapy boost; LDR-BB = low-dose-rate brachytherapy boost; sHR = subdistribution hazard ratio.

* *P* values calculated with Wald test.

Functional outcomes

There was no statistically significant difference in mean EPIC-26 urinary incontinence scores between EBRT monotherapy, HDR-BB, and LDR-BB (86.2, 86.0, and 87.0, respectively; $P = .304$) (Table 3).

There were statistically significant differences in the mean EPIC-26 urinary irritation/obstruction scores ($P < .001$). Men who received EBRT monotherapy had the highest mean scores (83.8) (ie, better function), followed by men receiving HDR-BB (78.9) and men who had LDR-BB (72.2). Post hoc pairwise tests demonstrated that the differences between the EBRT monotherapy group and both brachytherapy boost groups were statistically significantly different, without showing a statistically significant difference between HDR-BB and LDR-BB. The difference between LDR-BB and EBRT monotherapy met the threshold to be clinically important. However, the confidence interval surrounding the mean difference between HDR-BB and EBRT monotherapy was too wide to be conclusive.

The LDR-BB group had significantly worse mean EPIC-26 bowel scores (77.3) (ie, worse function) than the EBRT monotherapy group (84.4) and the HDR-BB group (85.8). Post hoc pairwise tests confirmed that the mean bowel score was statistically significantly lower in the LDR-BB group than the EBRT monotherapy or HDR-BB groups. These differences met the threshold required to be clinically important.

Cancer outcomes

Table 2 and Figure 3 show that the 5-year cumulative incidences of SREs and PCSM were different between the treatment groups. Post hoc pairwise tests demonstrated that HDR-BB had a statistically significantly lower SRE incidence (sHR, 0.72; 95% CI, 0.54-0.97) and lower PCSM (sHR, 0.75; 95% CI, 0.60-0.94) than EBRT monotherapy, without showing a difference between LDR-BB and either EBRT monotherapy or HDR-BB.

Discussion

To our knowledge, this is the largest observational study comparing toxicity, functional outcomes and cancer outcomes after HDR-BB, LDR-BB, and EBRT monotherapy for men with intermediate-risk, high-risk, and locally advanced prostate cancer. We used data from the National Prostate Cancer Audit to include all men treated with radical radiation therapy in the English National Health Service between 2010 and 2016 and reported functional outcomes using results from a national patient-reported outcome survey.

We found that LDR-BB was associated with worse GI toxicity at 5 years compared with either HDR-BB or EBRT monotherapy. The validity of this finding was supported by the results from the National Prostate Cancer Audit patient survey, in which differences in bowel function were large enough to be clinically important to patients. It has been reported that HDR brachytherapy has a greater consistency of dose distribution for target volume coverage and normal tissue sparing compared with LDR brachytherapy, and is also not subject to seed migration.[39]

Furthermore, men who received a BB, irrespective of type, were more likely to experience GU toxicity at 5 years compared with men who received EBRT monotherapy.

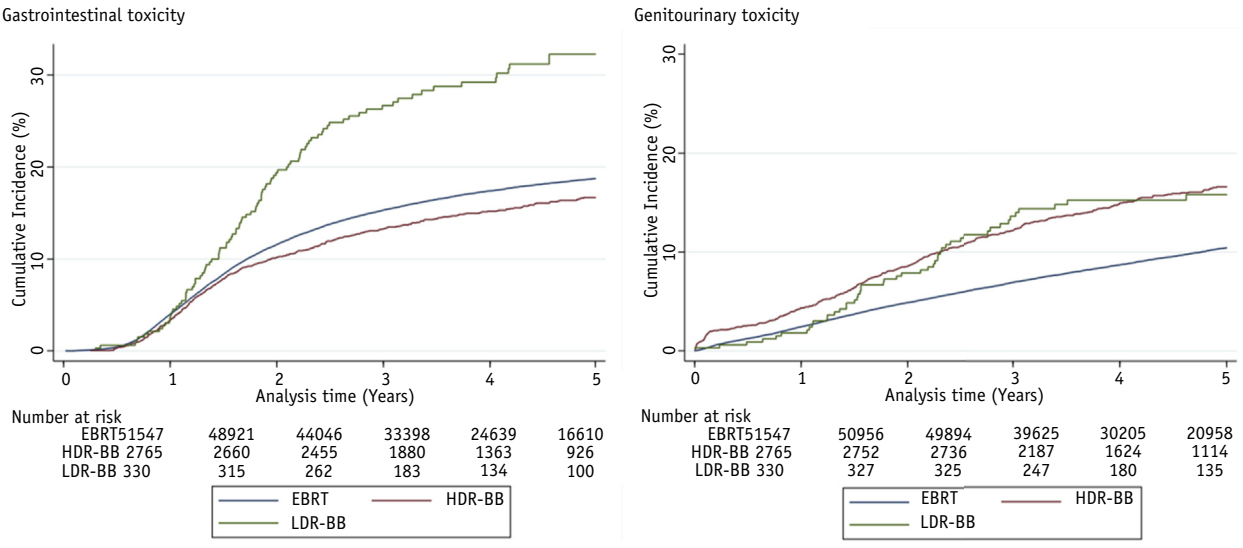


Fig. 2. Cumulative incidence of grade 2 or higher gastrointestinal and genitourinary toxicity after external beam radiation therapy monotherapy, high-dose-rate brachytherapy boost, or low-dose-rate brachytherapy boost.

HDR-BB was also associated with a lower cumulative incidence of both SREs and PCSM at 5 years compared with EBRT monotherapy.

Comparison with other studies

Our finding that LDR-BB has poorer GI and GU outcomes compared with EBRT monotherapy is consistent with results from the 2017 Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT) study, which used permanent Iodine-125 seeds. However, the trend towards worse GI toxicity in the ASCENDE-RT study was nonsignificant.[7] An older RCT of LDR-BB, which used temporary Iridium-192 wires, also found worse GI toxicity after LDR-BB but did not show any difference in GU toxicity.[7,8]

The single RCT and comparative observational data of HDR-BB (delivered with Iridium-192 afterloading) suggest that HDR-BB is at least comparable to EBRT monotherapy with respect to GI toxicity, with some data concluding that HDR-BB has a better GI toxicity profile.[3,17-19] Our findings support these data where toxicity of at least grade 2 was similar, and toxicity of at least grade 3 was lower, after HDR-BB compared with EBRT monotherapy. Regarding GU toxicity, results were comparable between the groups.[3-5] Although our results show that urinary irritation/obstruction domain scores were worse after HDR-BB, functional differences were inconclusive with respect to their clinical importance and significant differences observed in GU toxicity may not therefore translate into meaningful differences for all patients.[36]

Only one observational trial of 287 men has directly compared men receiving HDR-BB and LDR-BB with respect

Table 3 Functional outcomes in 11,676 patients who received EBRT monotherapy, HDR-BB, or LDR-BB

EPIC-26 domain	No.	Mean EPIC-26 score (95% CI)	Adjusted difference in means (95% CI)	*P* value*
Urinary (incontinence)				
EBRT monotherapy	10,912	86.2 (85.8-86.5)	0	.304
HDR-BB	683	86.0 (84.5-87.5)	-0.95 (-3.33-1.43)	
LDR-BB	81	87.0 (82.6-91.5)	-1.58 (-3.95-0.79)	
Urinary (irritation/obstruction)				
EBRT monotherapy	10,912	83.8 (83.5-84.2)	0	<.001
HDR-BB	683	78.9 (77.4-80.3)	-5.30 (-8.13 to -2.46)	
LDR-BB	81	72.2 (66.9-77.5)	-12.91 (-20.38 to -5.44)	
Bowel				
EBRT monotherapy	10,912	84.4 (84.1-84.8)	7.25 (4.97-9.54)	
HDR-BB	683	85.8 (84.4-87.2)	8.76 (5.52-12.00)	
LDR-BB	81	77.3 (72.2-82.5)	0	<.001

Abbreviations: CI = confidence interval; EBRT, external beam radiation therapy; EPIC-26 = Expanded Prostate Cancer Index Composite 26-item version; HDR-BB = high-dose-rate brachytherapy boost; LDR-BB = low-dose-rate brachytherapy boost.

* *P* values calculated with Wald test.

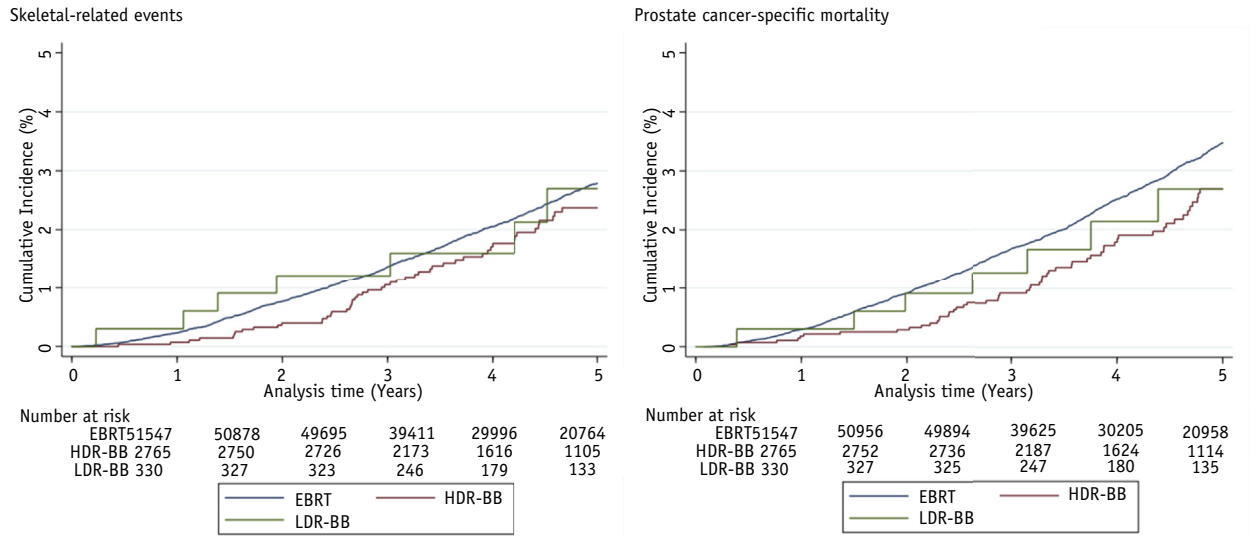


Fig. 3. Cumulative incidence of skeletal-related events and prostate cancer-specific mortality after external beam radiation therapy monotherapy, high-dose-rate brachytherapy boost, or low-dose-rate brachytherapy boost.

to toxicity. That trial supports our findings, with LDR-BB having worse GI toxicity (≥ grade 3) compared with HDR-BB (cumulative incidence of 8% and 4%, respectively). However, differences did not reach statistical significance.[16]

Two of the 3 RCTs discussed were conducted before 2012 when lower radiation doses (55 and 66 Gy) and older 4-field or 3-dimensional-conformal techniques were used. Both these trials showed better biochemical progression-free survival after a BB compared with EBRT monotherapy in which the brachytherapy type used was HDR-BB[3,17-19] and LDR-BB (using temporary Iridium-192 wires).[7,8] In contrast to our results, both trials did not find differences in PCSM even after a median follow-up period of 14 years. The third trial, conducted using higher doses (78 Gy) within the EBRT monotherapy group, also found that men receiving LDR-BB, using permanent Iodine-125 seeds, had better biochemical progression-free survival after a median follow-up of 6.5 years.[6] A single-center observational study of 287 men, directly comparing men receiving HDR-BB (2007-2012) and LDR-BB (1996-2007), concluded that LDR-BB may provide more effective prostate-specific antigen control at 5 years than HDR-BB.[16] Low patient numbers within the LDR-BB group in our study limited definitive conclusions with respect to cancer outcomes compared with either HDR-BB or EBRT monotherapy.

In support of other observational studies, we found a difference in cancer outcomes at 5 years between EBRT monotherapy and HDR-BB.[9-15] Five years is a relatively short timeframe to observe differences in prostate cancer outcomes, given that SREs and PCSM are rare events, and the potential benefit of HDR-BB may become more apparent with longer follow-up.

Strengths and limitations

This study includes a contemporary national population, which strengthens the generalizability of its results. In addition, more than 90% of the patients who receive radiation therapy in England are treated within the National Health Service, and these episodes are collected within the RTDS. Thus, all of the men receiving a recognized radiation therapy regimen during the study period were included in the study.[40] We are therefore confident that the majority of men who received LDR-BB within the study period were included but, because of its less frequent use in England compared with HDR-BB, this group had relatively lower patient numbers.

Another major strength of this study was that the outcome indicators are not based on clinician reporting.[29,32] The toxicity indicators were developed to include both diagnostic and procedure codes, which maximizes their specificity and minimizes the risk of misclassification bias. Furthermore, toxicity results of at least grade 3 aligns well with the overall toxicity results (≥ grade 2) across treatment groups. Finally, the agreement between the patient-reported outcome measures and the toxicity measures derived from national electronic health care data enhances the robustness of our conclusions.

All comparisons of toxicity and cancer outcomes between the treatment groups were adjusted for differences in patient and tumor characteristics, but data relating to prostate-specific antigen at diagnosis and androgen deprivation therapy use were not available. Both the long-term use of androgen deprivation and baseline bone mineral density can contribute to SREs and, therefore, these may represent potential confounders for this outcome. Furthermore, using these data sets, it was also not possible

to adjust for the heterogeneity in the planning techniques used within each treatment group or the volume of tissue irradiated. However, we have adjusted for the use of intensity-modulated radiation therapy and have information on the inclusion of pelvic lymph nodes within the treatment field, which could affect outcome.

Patients in the HDR-BB and LDR-BB groups tended to be younger, healthier, more affluent, and less likely to have had a prior GI procedure than those in the EBRT monotherapy group. Men receiving a BB are also selected based on their baseline urinary function. In other words, any residual confounding will have led to an overestimation of functional outcomes in men who received a BB, and the true effect of BB on GI and GU toxicity may be even greater than is reflected in the differences we report. Conversely, patients in the HDR-BB group had more advanced cancer than those in the EBRT monotherapy group, which makes it unlikely that residual confounding is an explanation for the better cancer outcomes observed with HDR-BB.

The patient-reported functional outcomes, measured 18 months after diagnosis, could not be adjusted for baseline function. However, we included GI and GU procedures in the year before prostate cancer diagnosis, which can be considered as proxy measures of baseline GI and GU function. Prostate size also has an influence on toxicity but is not collected within our data sources.

We also relied on the accuracy of the clinical coding in the administrative hospital data. However, the accuracy of these data has been shown to be high when compared with clinical notes.[41] The methods used in this article accounted for the fact that brachytherapy episodes, doses, and type were not routinely recorded in the RTDS (47%), and treatment patterns according to patient RTDS and HES records were used to ascertain the brachytherapy type used. A case note review at a single LDR brachytherapy center has shown that this coding framework can reliably identify brachytherapy episodes. Finally, some of the adjustment variables also had missing values, but we believe that multiple imputation was able to limit the affect of any potential confounding.

Conclusion

Adding a BB increases the toxicity of radiation therapy in prostate cancer patients in the first 5 years after treatment. However, our findings also suggest that HDR-BB may improve cancer outcomes compared with EBRT monotherapy. If a BB is considered, HDR-BB is preferable over LDR-BB, given its lower rate of GI toxicity. It is still unknown which type of BB is most beneficial in terms of long-term cancer control, and a definitive RCT will be required to answer this question.

References

1. Gray PJ, Zietman AL. Dose-escalated radiotherapy for prostate cancer: is the sky the limit? *JAMA Oncol* 2015;1:883-884.
2. Dayes IS, Parpia S, Gilbert J, Julian JA, Davis IR, Levine MN, et al. Long-term results of a randomized trial comparing iridium implant plus external beam radiation therapy with external beam radiation therapy alone in node-negative locally advanced cancer of the prostate. *Int J Radiat Oncol Biol Phys* 2017;99:90-93.
3. Hoskin PJ, Motohashi K, Bownes P, Bryant L, Ostler P. High dose rate brachytherapy in combination with external beam radiotherapy in the radical treatment of prostate cancer: initial results of a randomised phase three trial. *Radiother Oncol* 2007;84:114-120.
4. Hoskin PJ, Rojas AM, Bownes PJ, Lowe GJ, Ostler PJ, Bryant L. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. *Radiother Oncol* 2012;103:217-222.
5. Hoskin PJ, Rojas AM, Ostler PJ, Hughes R, Lowe GJ, Bryant L. Quality of life after radical radiotherapy for prostate cancer: longitudinal study from a randomised trial of external beam radiotherapy alone or in combination with high dose rate brachytherapy. *Clin Oncol (R Coll Radiol)* 2013;25:321-327.
6. Morris WJ, Tyldesley S, Rodda S, Halperin R, Pai H, McKenzie M, et al. Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT Trial): an analysis of survival endpoints for a randomized trial comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2017;98:275-285.
7. Rodda S, Tyldesley S, Morris WJ, Keyes M, Halperin R, Pai H, et al. ASCENDE-RT: an analysis of treatment-related morbidity for a randomized trial comparing a low-dose-rate brachytherapy boost with a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2017;98:286-295.
8. Sathya JR, Davis IR, Julian JA, Guo Q, Daya D, Dayes IS, et al. Randomized trial comparing iridium implant plus external-beam radiation therapy with external-beam radiation therapy alone in node-negative locally advanced cancer of the prostate. *J Clin Oncol* 2005;23:1192-1199.
9. Deutsch I, Zelefsky MJ, Zhang Z, Mo Q, Zaider M, Cohen G, et al. Comparison of PSA relapse-free survival in patients treated with ultra-high-dose IMRT versus combination HDR brachytherapy and IMRT. *Brachytherapy* 2010;9:313-318.
10. Kent AR, Matheson B, Millar JL. Improved survival for patients with prostate cancer receiving high-dose-rate brachytherapy boost to EBRT compared with EBRT alone. *Brachytherapy* 2019;18:313-321.
11. Wedde TB, Smastuen MC, Brabrand S, Fossa SD, Kaasa S, Tafjord G, et al. Ten-year survival after high-dose-rate brachytherapy combined with external beam radiation therapy in high-risk prostate cancer: a comparison with the Norwegian SPCG-7 cohort. *Radiother Oncol* 2019;132:211-217.
12. Johnson SB, Lester-Coll NH, Kelly JR, Kann BH, Yu JB, Nath SK. Brachytherapy boost utilization and survival in unfavorable-risk prostate cancer. *Eur Urol* 2017;72:738-744.
13. King MT, Yang DD, Muralidhar V, Mahal B, Butler S, Devlin PM, et al. A comparative analysis of overall survival between high-dose-rate and low-dose-rate brachytherapy boosts for unfavorable-risk prostate cancer. *Brachytherapy* 2019;18:186-191.
14. Marina O, Gustafson GS, Kestin LL, Brabbins DS, Chen PY, Ye H, et al. Comparison of dose-escalated, image-guided radiotherapy vs. dose-escalated, high-dose-rate brachytherapy boost in a modern cohort of intermediate-risk prostate cancer patients. *Brachytherapy* 2014;13:59-67.
15. Kishan AU, Cook RR, Ciezki JP, Ross AE, Pomerantz MM, Nguyen PL, et al. Radical prostatectomy, external beam radiotherapy, or external beam radiotherapy with brachytherapy boost and disease progression and mortality in patients with Gleason score 9-10 prostate cancer. *JAMA* 2018;319:896-905.
16. Slevin F, Rodda SL, Bownes P, Murray L, Bottomley D, Wilkinson C, et al. A comparison of outcomes for patients with intermediate and high risk prostate cancer treated with low dose rate and high dose rate

brachytherapy in combination with external beam radiotherapy. *Clin Transl Radiat Oncol* 2020;20:1-8.
17. Fang FM, Wang YM, Wang CJ, Huang HY, Chiang PH. Comparison of the outcome and morbidity for localized or locally advanced prostate cancer treated by high-dose-rate brachytherapy plus external beam radiotherapy (EBRT) versus EBRT alone. *Jpn J Clin Oncol* 2008;38:474-479.
18. Soumarova R, Homola L, Perkova H, Stursa M. Three-dimensional conformal external beam radiotherapy versus the combination of external radiotherapy with high-dose rate brachytherapy in localized carcinoma of the prostate: comparison of acute toxicity. *Tumori* 2007;93:37-44.
19. Mohammed N, Kestin L, Ghilezan M, Krauss D, Vicini F, Brabbins D, et al. Comparison of acute and late toxicities for three modern high-dose radiation treatment techniques for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2012;82:204-212.
20. National Prostate Cancer Audit. Annual report 2019: results of the NPCA prospective audit in England and Wales for men diagnosed from 1 April 2017 - 31 March 2018. Available at: https://www.npca.org.uk/reports/npca-annual-report-2019/. Accessed January 2020.
21. National Cancer Intelligence Network. National cancer data repository. Available at: http://www.ncin.org.uk/collecting_and_using_data/national_cancer_data_repository/. Accessed December 11, 2016.
22. National Cancer Registration and Analysis Service. National radiotherapy dataset (RTDS). Available at: http://www.ncin.org.uk/collecting_and_using_data/rtds. Accessed December 11, 2017.
23. National Health Service. Hospital episode statistics. Available at: http://www.hesonline.nhs.uk. Accessed January 15, 2017.
24. World Health Organisation. International statistical classification of diseases and related health problems (10th Revision). Available at: http://www.who.int/classifications/icd/ICD10Volume2_en_2010.pdf. Accessed September 28, 2017.
25. National Health Service. OPCS-4 classification of interventions and procedures. Available at: http://www.digital.nhs.uk/article/1117/Clinical-Classifications. Accessed January 8, 2018.
26. National Prostate Cancer Audit. Annual report 2017: results of the NPCA prospective audit in England and Wales for men diagnosed from 1 April 2015 - 31 March 2016 (2017). Available at: http://www.npca.org.uk/content/uploads/2017/11/NPCA-2017-Annual-Report_final_211117.pdf. Accessed September 9, 2018.
27. National Institute for Health and Care Excellence. Prostate cancer: diagnosis and management (2019). Available at: https://www.nice.org.uk/guidance/ng131/resources/prostate-cancer-diagnosis-and-management-pdf-66141714312133. Accessed July 17, 2019.
28. Szymanski KM, Wei JT, Dunn RL, Sanda MG. Development and validation of an abbreviated version of the expanded prostate cancer index composite instrument for measuring health-related quality of life among prostate cancer survivors. *Urology* 2010;76:1245-1250.
29. Sujenthiran A, Nossiter J, Charman SC, Parry M, Dasgupta P, van der Meulen J, et al. National population-based study comparing treatment-related toxicity in men who received intensity modulated versus 3-dimensional conformal radical radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2017;99:1253-1260.
30. National Institutes of Health NCI. Common terminology criteria for adverse events (CTCAE). Available at: http://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed January 8, 2018.
31. University of Michigan. Scoring instructions for the Expanded Prostate Cancer Index Composite Short Form (EPIC-26) (2002). Available at: https://medicine.umich.edu/sites/default/files/content/downloads/Scoring%20Instructions%20for%20the%20EPIC%2026.pdf. Accessed May 14, 2019.
32. Parry MG, Cowling TE, Sujenthiran A, Nossiter J, Berry B, Cathcart P, et al. Identifying skeletal-related events for prostate cancer patients in routinely collected hospital data. *Cancer Epidemiol* 2019;63:101628.
33. Armitage JN, van der Meulen JH. Identifying co-morbidity in surgical patients using administrative data with the Royal College of Surgeons Charlson Score. *Br J Surg* 2010;97:772-781.
34. Ministry of Housing CLG. National Statistics: English indices of deprivation 2015. Available at: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015. Accessed May 26, 2020.
35. Fine JP, Gray RP. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496-509.
36. Skolarus TA, Dunn RL, Sanda MG, Chang P, Greenfield TK, Litwin MS, et al. Minimally important difference for the Expanded Prostate Cancer Index Composite Short Form. *Urology* 2015;85:101-105.
37. Dunn OJ. Multiple comparison among means. *J Am Stat Assoc* 1961;56:52-64.
38. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011;30:377-399.
39. Morton GC, Hoskin PJ. Brachytherapy: current status and future strategies — can high dose rate replace low dose rate and external beam radiotherapy? *Clin Oncol (R Coll Radiol)* 2013;25:474-482.
40. Aggarwal A, Lewis D, Sujenthiran A, Charman SC, Sullivan R, Payne H, et al. Hospital quality factors influencing the mobility of patients for radical prostate cancer radiation therapy: a national population-based study. *Int J Radiat Oncol Biol Phys* 2017;99:1261-1270.
41. Burns EM, Rigby E, Mamidanna R, Bottle A, Aylin P, Ziprin P, et al. Systematic review of discharge coding accuracy. *J Public Health (Oxf)* 2012;34:138-148.

7.2 Research Paper 7

Title: Patient-reported outcomes following external beam radiation therapy for prostate cancer with and without a high-dose rate brachytherapy boost: a national population-based study.

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SECTION A – Student Details

Student ID Number	LSH1800100	**Title**	Dr
First Name(s)	Matthew		
Surname/Family Name	Parry		
Thesis Title	Use of routinely collected hospital data to explore access to and outcomes from different radiotherapy treatment strategies for locally advanced prostate cancer: national population-based studies.		
Primary Supervisor	Professor Jan van der Meulen		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Radiotherapy & Oncology		
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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Designed the work, analysed and interpreted the data, drafted the article and approved the final version to be published.

SECTION E

Student Signature	M. Parry
Date	8/1/21

Supervisor Signature	J. van der Meulen
Date	8/1/21

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Original Article

Patient-reported functional outcomes following external beam radiation therapy for prostate cancer with and without a high-dose rate brachytherapy boost: A national population-based study

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ABSTRACT

Background and purpose: Little is known about the functional outcomes and health-related quality of life (HRQoL) following external beam radiation therapy (EBRT) combined with a high-dose rate brachytherapy boost (EBRT-BB) for the treatment of prostate cancer. We aimed to compare patient-reported outcomes of EBRT to those of EBRT-BB.

Methods and materials: Patients diagnosed with intermediate-risk, high-risk or locally advanced prostate cancer (April 2014 to September 2016), who received EBRT in the English National Health Service within 18 months of diagnosis and responded to a national patient questionnaire, were identified from the National Prostate Cancer Audit. Adjusted linear regression was used to estimate differences in functional EPIC-26 domains and HRQoL (EQ-5D-5L) between treatment groups. Non-inferiority of EBRT-BB was determined if the lower 95% confidence limit did not exceed the established minimal clinically important difference (MCID).

Results: Of the 13,259 included men, 12,503 (94.3%) received EBRT and 756 (5.7%) received EBRT-BB. EBRT-BB was non-inferior compared to EBRT for the urinary incontinence, sexual, bowel and hormonal EPIC-26 domains. EBRT-BB resulted in significantly worse urinary irritation/obstruction scores than EBRT (−6.1; 95% CI: −8.8 to −3.4) but uncertainty remains as to whether this difference is clinically important (corresponding MCID of 5).

Conclusions: There is no evidence to suggest that EBRT-BB results in any clinically important detriment in functional outcomes or HRQoL compared to men receiving EBRT only. Whilst statistically significantly worse urinary irritation/obstruction outcomes were reported in the EBRT-BB cohort, the threshold for a clinically significant difference was not exceeded and further research is required for confirmation.

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Advances in radiotherapy planning and treatment have allowed for higher doses to be delivered to the prostate without leading to worse treatment safety or tolerability [1].

Dose-escalation can also be achieved by using a brachytherapy boost (BB) in addition to external beam radiation therapy (EBRT). Three randomised controlled trials have compared EBRT with BB to EBRT only and the results suggest there is a benefit in terms of long-term biochemical cancer control but not with regards to overall survival [2–8]. Importantly however, the single study to use a high-dose rate (HDR) brachytherapy boost used lower doses of EBRT within the comparator arm (EBRT only) than those used currently [3–5].

Data from observational studies have reported further benefits of EBRT with BB for prostate cancer-specific mortality and a longer time to distant metastasis (low-dose rate [LDR] and HDR grouped together) [9]. A recently published cohort study has also reported superior overall survival of EBRT with HDR-BB compared to either EBRT with LDR-BB or EBRT only [10].

There remains a paucity of data available to understand treatment toxicities following EBRT with BB and patient-reported outcome measures (PROMs) have rarely been used to capture

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toxicity [11]. To date only two small studies have used PROMs to compare sexual function and health-related quality of life (HRQoL) in men receiving EBRT with BB or EBRT only and their results did not show any difference. Importantly, these studies did not include any measure of urinary or bowel function [5,12].

In this national study of 13,259 men, we used PROMs collected by the National Prostate Cancer Audit (NPCA) to quantify to what extent adding HDR-BB to EBRT in men with intermediate-risk, high-risk or locally advanced prostate cancer alters patient urinary, sexual, bowel and hormonal function compared to delivering EBRT only. We compared differences in PROMs against established minimal clinically important differences (MCID) in functional outcomes and used a non-inferiority approach to determine if adding HDR-BB had an impact that patients would identify as important.

Materials and methods

Patient population

This study used English cancer registry data [13], the National Radiotherapy Dataset (RTDS) [14] and Hospital Episode Statistics (HES) [15] linked at patient level to identify men who were diagnosed with prostate cancer between April 1, 2014 and September 30, 2016 and treated with EBRT. The International Classification of Diseases, 10th Edition [ICD-10] [16] code for prostate cancer "C61" in the cancer registry data was used to identify men with prostate cancer. The English cancer registry contains all new diagnoses of prostate cancer in England. 19,374 men receiving primary EBRT for non-metastatic prostate cancer were identified in the RTDS (Fig. 1). The RTDS and HES databases include all radiotherapy and inpatient hospital episodes that take place within the English NHS.

Prostate cancer risk was based on TNM stage, Gleason score, and PSA level according to a modified D'Amico risk stratification algorithm developed previously by the NPCA [17,18]. The cohort was restricted to intermediate-risk, high-risk or locally advanced prostate cancer by excluding men with low-risk prostate cancer (n = 167) and men of unknown risk group (n = 293). Men with a concomitant diagnosis of bladder cancer (n = 410) were also excluded.

The RTDS provided information on radiotherapy doses and number of attendances to classify each radiotherapy regimen. The radiation doses used to classify men into groups (EBRT only versus EBRT with HDR-BB) are also outlined in Fig. 1. If the brachytherapy type was unknown, it was assigned to LDR or HDR based on the type of brachytherapy offered at that radiotherapy centre. If the radiotherapy centre offered both LDR and HDR then brachytherapy type was classified as unknown. Men were excluded from the NPCA data set if the radiotherapy regimen (n = 949) was unknown, if a LDR-BB was used (n = 124), if the brachytherapy type was unknown (n = 30) or if there was > 3 months between radiotherapy and brachytherapy (n = 2).

Further exclusions were made for men who had moved/died/were ineligible (n = 176) or who had completed radiotherapy less than six months before the surveys were sent out (n = 113). Surveys were sent out to 17,110 men and 13,259 men responded (77.5%).

Patient surveys

The records of the patients included in the final cohort were linked to the NPCA patient survey (Supplementary Material). Patient surveys were mailed to men diagnosed with prostate cancer between April 1, 2014 and September 30, 2016 who received radical local treatment within 18 months of their prostate cancer diagnosis. Two reminders were sent to non-responders 3 and 6 weeks after the initial mailing. The questionnaire included the Expanded Prostate Cancer Index Composite 26-item version (EPIC-26) which is a validated instrument to measure quality of life related to prostate cancer according to urinary incontinence, urinary irritation/obstruction, sexual, bowel and hormonal domains [19]. Each domain contains between 4–7 items and scores were summarised for each domain on a scale of 0 to 100, with higher scores representing better function.

The questionnaire also included the EuroQol (EQ-5D-5L) which describes generic HRQoL based on five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Responses to these domains had five levels of severity ("no problems", "slight problems", "moderate problems", "severe problems" and "unable to/extreme problems"). An index score (0 – "death"; 1 – "perfect health") was calculated by matching the pattern of the five responses to a set of utilities from the general UK population [20].

As baseline EPIC-26 and EQ-5D-5L scores were not collected, the patient survey included three questions which asked patients to recall urinary, sexual and bowel function at the time of diagnosis. These recalled measures were captured on a 5-point scale from "no problem" to "large problem".

Study outcome

Primary outcomes were the five EPIC-26 domain scores and the EQ-5D-5L index score according to treatment (EBRT with HDR-BB versus EBRT only). Missing response data to individual items were handled according to specific guidelines for EPIC-26 and EQ-5D-5L, respectively [21,22].

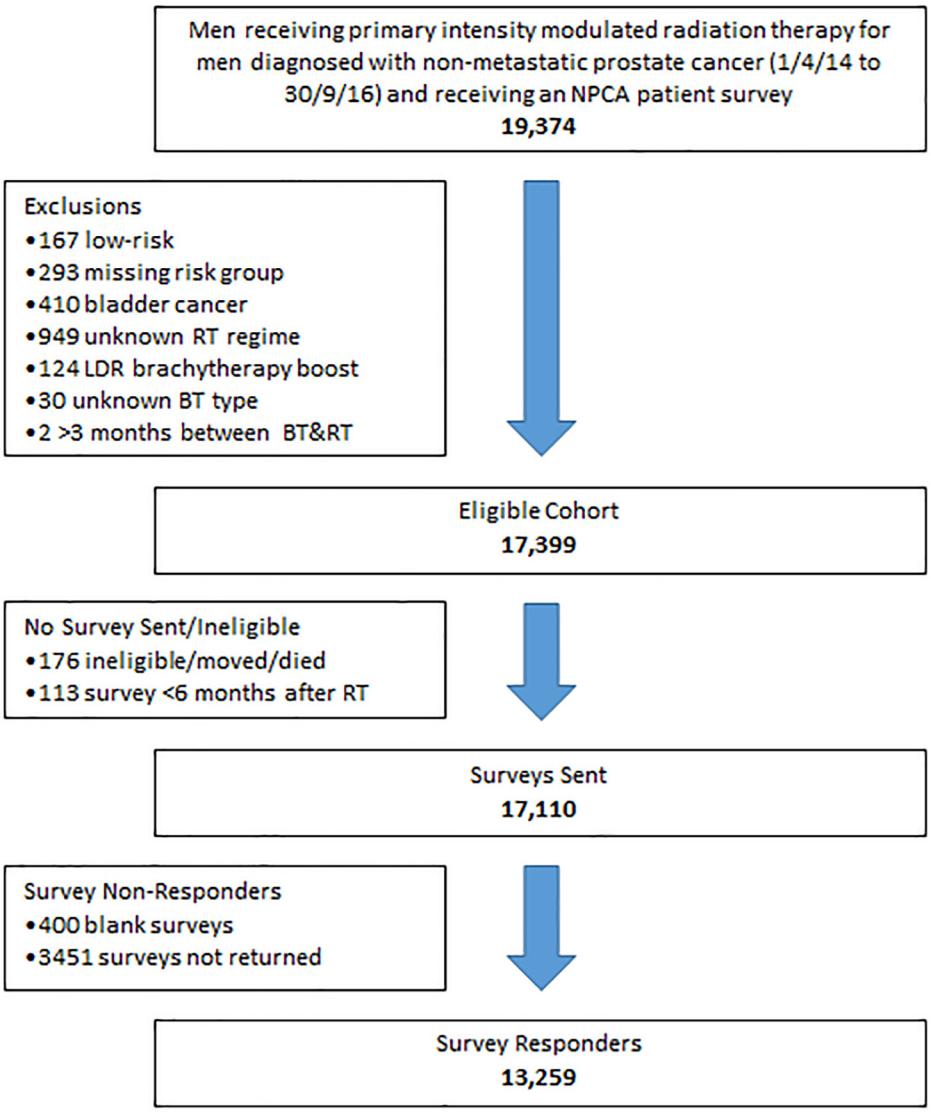
Explanatory and control variables

HES records were used to determine age, ethnicity, socioeconomic deprivation according to the Index of Multiple Deprivation [23], and the number of comorbid conditions according to the RCS Charlson Score [24]. T-stage, N-stage, M-stage, Gleason score and PSA were identified from the English cancer registry data. Information on androgen deprivation therapy (ADT) use and number of comorbid conditions was available from the patient survey. Comorbidity data from the patient surveys was used for the primary analysis. Comorbidity data based on the RCS Charlson score derived from HES was only used for the comparison between survey responders and non-responders. The RTDS OPCS-4 code "X671" [25] was used to identify the men receiving intensity modulated radiation therapy (IMRT).

We have previously developed a coding framework to identify gastrointestinal (GI) and genitourinary (GU) toxicity within HES which was based on codes for lower GI endoscopy or procedures of the lower urinary tract [26]. We used this framework to estimate baseline GI and GU function for each patient according to whether a GI or GU procedure was carried out up to one year before the start of radiotherapy.

Statistical analysis

Multivariable linear regression was used to estimate differences in study outcomes between the treatment groups, where negative differences represent poorer outcomes in patients receiving EBRT with HDR-BB than patients receiving EBRT only. Analyses were adjusted for baseline patient characteristics: treatment year, age, number of comorbidities, socioeconomic deprivation status, ethnicity, pre-treatment GI procedures or GU procedures, cancer risk profile (intermediate-risk, high-risk or locally advanced disease),



Included fractionated regimes:

EBRT only cohort RT regimen (Gy/Fractions)	BB cohort RT regimen (Gy/Fractions)	BB cohort BT regimen (Dose)
72-79/35-49	36-39/15	<30 (HDR)
72/32	43-47/22-25	≥100 (LDL) - excluded
70/35	50/28	
69/37		
50-60/16 or 19-20 (hypofractionated)		

Fig. 1. Patient chart of cohort selection.

IMRT use, ADT use, and time between the start of radiotherapy treatment and the patient survey (6–12, 12–18 and > 18 months).

Previous publications from our research group have shown that treatment region (prostate-only versus prostate and pelvic lymph nodes radiation) and radiotherapy regimen (standard fractionation versus hypofractionation) do not alter functional outcomes and these treatment characteristics were therefore not included in the adjustment model [27,28]. A random intercept was modelled for each hospital to adjust for clustering of outcomes within hospitals.

For each of the five EPIC-26 domains, an additional analysis was carried out which also included the patients' recalled baseline urinary, sexual and bowel function in the adjustment model.

Missing values for baseline characteristics (ethnicity, ADT use, T-stage, N-stage, PSA and Gleason score) and outcomes were imputed using multiple imputation by chained equations to

include all survey responders. 20 data sets were created and Rubin's rules used to combine study estimates.

Adjusted differences in EPIC-26 domain scores and EQ-5D-5L were interpreted as "clinically important" based on previously reported MCIDs [29,30]. A MCID refers to the smallest difference that a patient would describe as important and which would impact on a patient's clinical management [31]. The MCIDs used for the EPIC-26 urinary incontinence, urinary irritation/obstruction, sexual, bowel and hormonal domains were 6, 5, 10, 4 and 4, respectively as outlined by Skolarus et al [29]. The MCID used for the EQ-5D-5L was 0.08 as outlined by Pickard et al [30].

P values smaller than 0.05 were considered to indicate a statistically significant result. Non-inferiority of adding HDR-BB was analysed by comparing the 95% confidence intervals (CI) of the adjusted differences against the corresponding MCIDs. We concluded that "non-inferiority" was demonstrated if the lower limit of a 95% CI did not exceed the corresponding MCID and that "inferiority" was demonstrated if the upper 95% CI limit exceeded the MCID [32]. Results were interpreted as "inconclusive" if the MCID fell within the 95% CI.

All analyses were performed using STATA v.14 (StataCorp. 2015. Stata Statistical Software (College Station, TX, USA)).

Results

Survey response

13,259 of the 17,110 men (77.5%) who received a patient survey responded (Fig. 1). Responders were more likely to be older, to be of white ethnicity, to be from a less socially deprived area and to have fewer comorbidities than non-responders. There was no difference in response rates between men who had EBRT with HDR-BB or EBRT only (Supplementary Material).

Patient population

Of the 13,259 men included in the study, 756 (5.7%) received EBRT with HDR-BB (Table 1). The median age was 72 years (range: 44 to 90) and 81.0% had at least one reported comorbidity. The majority of men had locally advanced or high-risk disease (n = 8,941, 67.4%).

Compared to men receiving EBRT only, men having EBRT with HDR-BB were more likely to be younger (age $\leq$ 70 years: 55.5% vs 36.9%), have no comorbidities (25.3% vs 18.6%), to be of a lower socioeconomic deprivation status (least deprived: 25.2% vs 24.2%), have locally advanced disease (79.4% vs 66.7%) and to have received ADT (80.4% vs 73.6%). However, they were less likely to have a urinary procedure within 1 year prior to radiotherapy (14.3% vs 21.2%).

64.8% of the EBRT only group received a standard regimen (median total dose 74 Gy in 37 fractions) with the remaining 35.2% receiving a hypofractionated regimen (median dose 60 Gy in 20 fractions). The most common EBRT doses in the EBRT with HDR-BB group were 46 Gy in 23 fractions (44.7%) or a hypofractionated regimen of 37.5 Gy in 15 fractions (40.1%). The majority of men who were given a HDR-BB received a dose of 15 Gy in 1 fraction (84.5%) and received it before EBRT (78.1%), although treatment order was unknown in 6.6% of cases.

Time from diagnosis to radiotherapy varied slightly between the treatment groups with a median time of 5.4 months (interquartile range [IQR]: 4.6 to 6.9) for EBRT only and 6.1 months (IQR: 4.9 to 7.7) for the EBRT with HDR-BB group. Median time from radiotherapy to survey completion did not vary between groups and was 15.6 months (IQR: 13.5 to 19.7).

Outcome measures

EPIC-26 domain scores were relatively high for urinary (80.7–86.2) and bowel domains (85.9–87.0) and relatively low for the sexual domain (17.9–18.0) in both treatment groups (Table 2).

There were no significant differences in urinary incontinence, sexual, bowel and hormonal EPIC-26 domain scores between the treatment groups (adjusted differences: −1.5, 0.1, 1.4 and 1.3, respectively; all *P* values > 0.10). The lower limits of the 95% CI of all these four EPIC-26 domains did not exceed the corresponding MCID and EBRT with HDR-BB can therefore be considered as non-inferior compared to EBRT only (Fig. 2).

EBRT with HDR-BB had significantly worse urinary irritation/obstruction EPIC-26 domain scores than EBRT only (adjusted difference: −6.1; 95% CI: −8.8 to −3.4). However, this result was inconclusive with respect to non-inferiority because the MCID fell within the 95% CI (Table 2 and Fig. 2).

Men receiving EBRT with HDR-BB had statistically significantly better HRQoL scores (or higher mean adjusted EQ-5D-5L scores) than men receiving EBRT only (adjusted difference: 0.03; 95% CI: 0.02 to 0.04) (Table 2 and Fig. 2).

Additional analysis

Men who underwent EBRT with HDR-BB were more likely to recall their baseline urinary, sexual and bowel function as "no problem" compared to men who underwent EBRT only (urinary function: 38.6% versus 29.0%, $P < 0.001$; sexual function: 45.1% versus 42.8%, $P = 0.114$; bowel function: 81.0% versus 71.7%, $P < 0.001$).

Including these variables in the linear regression models had little impact on the results observed between treatment groups. When the recalled baseline variables were included in the regression model, we found that the difference in urinary irritation/obstruction and incontinence scores between treatment groups both increased, but only to a small degree, from −6.1 to −7.6 and −1.5 to −3.1, respectively. Although inferiority was then demonstrated for the urinary irritation/obstruction domain, the overall impact of including recalled baseline function within the adjustment models was small. Sub-group analyses were performed for men who recalled that they had "no problem" with their baseline urinary and sexual function. Adjusted differences between treatment groups were only marginally larger for men with normal baseline urinary function with respect to urinary irritation/obstruction scores (-6.1 to −6.7) and urinary incontinence scores (−1.5 to −2.9) and interpretation remained the same as for the main analysis. This was also the case for men with normal baseline sexual function and their post-treatment sexual function scores (0.0 to −0.5). Interpretation of findings also remained the same for men who completed their patient survey $\geq$24 months after treatment. Adjusted differences between treatment groups remained insignificant for urinary incontinence, sexual function, hormonal function and bowel function domains with minimal change in urinary irritation/obstruction scores (-6.1 to −7.3) and HRQoL scores (0.03 to 0.04).

Discussion

Our PROMs analysis indicates that EBRT with HDR-BB is non-inferior to EBRT with respect to urinary incontinence, sexual, bowel and hormonal EPIC-26 domains and HRQoL for men with intermediate and high-risk prostate cancer. Our results also showed that urinary irritation/obstruction scores were worse for men receiving EBRT with HDR-BB compared to men receiving EBRT only but results were inconclusive as to whether these results represented inferiority.

Table 1
Patient, tumour and treatment characteristics by radiotherapy treatment.

	EBRT only		EBRT with HDR-BB		Total	
	n	%	*N*	%	*n*	%
No. of patients	12,503	94.3	756	5.7	13,259	100
Treatment year						
2014	2,482	19.9	151	20.0	2,633	19.9
2015	4,255	34.0	258	34.1	4,513	34.0
2016	5,766	46.1	347	45.9	6,113	46.1
Age (years)						
≤60	493	3.9	67	8.9	560	4.2
61–70	4,126	33.0	352	46.6	4,478	33.8
71–80	7,102	56.8	330	43.7	7,432	56.1
>80	782	6.3	7	0.9	789	6.0
Comorbidities						
0	2,330	18.6	191	25.3	2,521	19.0
1	3,781	30.2	276	36.5	4,057	30.6
≥2	6,392	51.1	289	38.2	6,681	50.4
Socioeconomic deprivation						
1 (least deprived)	3,030	24.2	193	25.5	3,223	24.3
2	3,041	24.3	221	29.2	3,262	24.6
3	2,708	21.7	177	23.4	2,885	21.8
4	2,127	17.0	99	13.1	2,226	16.8
5 (most deprived)	1,597	12.8	66	8.7	1,663	12.5
Ethnicity						
White	11,217	95.9	715	97.7	11,932	96.0
Mixed	29	0.2	1	0.1	30	0.2
Asian	153	1.3	3	0.4	156	1.3
Black	213	1.8	12	1.6	225	1.8
Other	79	0.7	1	0.1	80	0.6
Missing	812		24		836	
Genitourinary procedure 1 year prior to radiotherapy						
No	9,850	78.8	648	85.7	10,498	79.2
Yes	2,653	21.2	108	14.3	2,761	20.8
Gastrointestinal procedure 1 year prior to radiotherapy						
No	11,852	94.8	719	95.1	12,571	94.8
Yes	651	5.2	37	4.9	688	5.2
Cancer risk profile						
High-risk or locally advanced	8,341	66.7	600	79.4	8,941	67.4
Intermediate risk	4,162	33.3	156	20.6	4,318	32.6
Radiotherapy type						
3D conformal	563	4.5	150	19.8	713	5.4
IMRT	11,940	95.5	606	80.2	12,546	94.6
Androgen deprivation						
No	3,305	26.4	148	19.6	3,453	26.0
Yes	9,198	73.6	608	80.4	9,806	74.0
Time between radiotherapy and survey (months)						
6–11	1,378	11.0	125	16.5	1,503	11.3
12–18	7,006	56.0	389	51.5	7,395	55.8
≥18	4,119	32.9	242	32.0	4,361	32.9

National clinical guidelines in the UK recommend the consideration of EBRT with HDR-BB in this patient group, but little is known about its toxicity [33]. Our results provide information that is highly relevant to patients but follow-up beyond 16 months is required to make a full assessment of late toxicity.

This is the first study to use a comprehensive validated PROMs instrument which included both functional domains and a measure of HRQoL to compare EBRT with HDR-BB and EBRT only. The use of national data ensures that the results are generalisable across all radiotherapy centres in the English National Health Service and representative of a contemporary treatment strategy in the UK and in other high-income countries with an advanced healthcare system.

Comparison with other studies

Only two studies have previously reported PROMs to compare the toxicity of EBRT with HDR-BB and EBRT only [5,12]. Both studies only reported sexual function and there were no measures of urinary function, bowel function or HRQoL. Only one of these studies represented contemporary patients receiving IMRT exclusively [12]. This single-centre study found no significant differences in the International Index of Erectile Function scores reported by 470 men who had EBRT only and 400 men who had EBRT with BB. The second study was one of the three randomised controlled trials that evaluated BB within the experimental arm [5]. This study reported no differences in sexual function, which was derived from the Functional Assessment of Cancer Therapy (FACT) questionnaire, over a 10.5 year follow-up.

Clinician-reported toxicity is more frequently reported in studies of HDR-BB than toxicity derived from PROMs. Results from the only randomised controlled trial of HDR-BB indicate that acute and late GU toxicity were comparable between EBRT with HDR-BB and EBRT only groups [3,4]. However, of the two trials using LDR-BB only ASCENDE-RT showed higher acute and late GU morbidity with LDR-BB compared to EBRT, which may be explained by the use of permanent Iodine-192 seeds (instead of a temporary Iridium-192 implant) and the use of a higher EBRT dose in the control arm (78 Gy versus 66 Gy) [7,8].

Observational data of EBRT with HDR-BB and EBRT with a mixed BB cohort (both HDR and LDR) highlight that although EBRT with BB confers initially worse acute (up to 3 or 6 months after

Table 2
Relationship between patient-reported outcomes after radiotherapy (EBRT with HDR-BB versus EBRT only): overall domain scores for EPIC-26 and EQ-5D-5L and adjusted differences.

	EBRT only	EBRT with HDR-BB	EBRT with HDR-BB versus EBRT only	
			Adjusted difference* (95% CI)	*P*
N (%)	12,503 (94.3)	756 (5.7)		
EPIC-26				
Urinary (incont.)				
Mean (SD)	86.2 (19.3)	85.6 (19.9)	−1.5 (−3.5 to 0.5)	0.133
Missing (*n*)	1687	99		
Urinary (irrit./obst.)				
Mean (SD)	86.3 (15.2)	80.7 (18.4)	−6.1 (−8.8 to −3.4)	**<0.001**
Missing (*n*)	2516	128		
Sexual				
Mean (SD)	17.9 (21.5)	18.0 (21.6)	0.0 (−2.6 to 2.7)	0.971
Missing (*n*)	1029	37		
Bowel				
Mean (SD)	85.9 (18.3)	87.0 (17.2)	1.4 (−0.7 to 3.5)	0.206
Missing (*n*)	1817	78		
Hormonal				
Mean (SD)	70.5 (23.3)	70.4 (22.8)	1.3 (−1.7 to 4.3)	0.407
Missing (*n*)	1546	63		
HEALTH-RELATED QoL				
EQ-5D-5L				
Mean (SD)	0.84 (0.19)	0.89 (0.15)	0.03 (0.02 to 0.04)	**<0.001**
Missing (*n*)	368	13		

Abbreviations: EBRT – External Beam Radiation Therapy; HDR – High-Dose-Rate; CI – Confidence Interval; QoL – Quality of Life. Note: Underlined and bolded *p* values represent statistical significance and clinical importance, respectively.
* Negative differences represent poorer outcomes in patients receiving EBRT with HDR-BB.

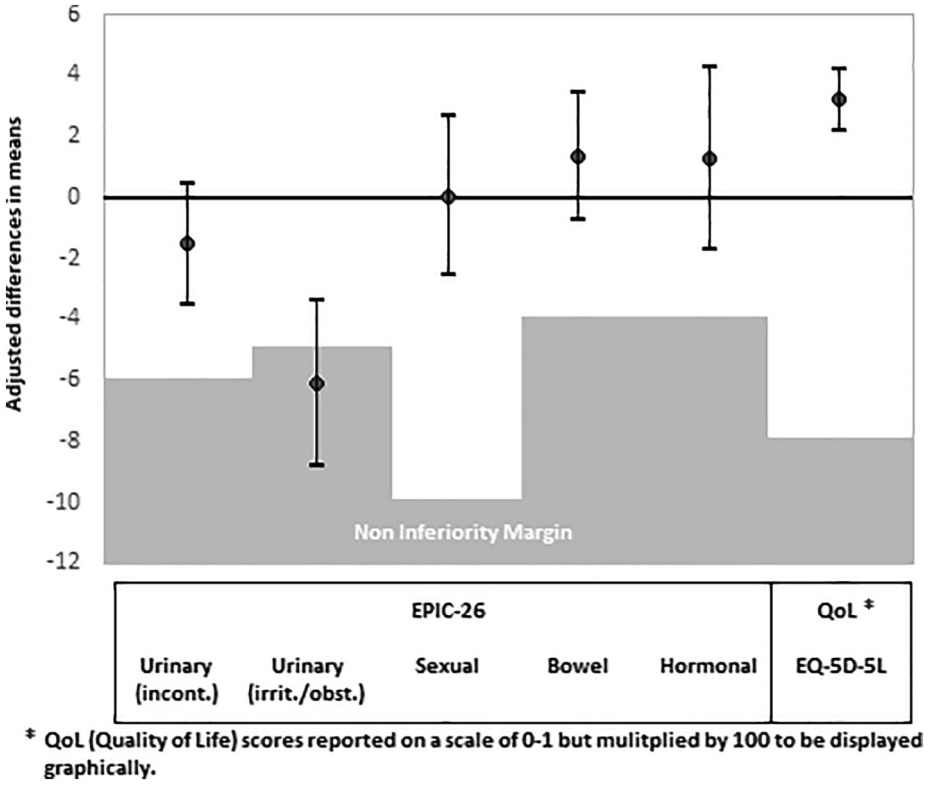


Fig. 2. Relationship between patient-reported outcomes after radiotherapy treatment (EBRT only versus EBRT with HDR-BB). Adjusted differences in means for EPIC-26 and EQ-5D-5L domain scores with 95% confidence intervals and non-inferiority margins. Negative differences represent poorer outcomes in patients receiving EBRT with HDR-BB.

treatment) GU toxicity, the majority of this acute toxicity is only transient [12,34]. EBRT with HDR-BB has previously been associated with a ten-fold increase in the occurrence of urethral strictures compared to EBRT only (16.8% versus 1.9% at five years, respectively) but more recent observations have shown that improvements in image guidance software have been able to better protect the urethra against the development of strictures following HDR-BB [34,35].

Regarding GI toxicity, one trial found rectal discharge to be more prevalent in the EBRT only group than the EBRT with HDR-BB group up to 12 weeks after treatment [3]. This result is in keeping with observational studies showing worse acute and late GI

toxicity for men receiving EBRT only [34,36,37]. In addition to the higher radiotherapy doses used for the men receiving EBRT only, it is likely that the older techniques used in these studies (3D conformal radiotherapy) were also contributing to these higher rates. For example, men receiving a higher dose of IMRT (86.4 Gy) in the EBRT only arm in one study did not experience worse acute GI toxicity compared to EBRT with BB [12].

Strengths and limitations

The main strengths of this study include the high questionnaire response rate (77.5%), the use of a contemporary national population and the use of a comprehensive validated instrument for collecting PROMs (EPIC-26 and EQ-5D-5L).

Responders tended to be older, of white ethnicity, from a less socially deprived area and had fewer comorbidities than non-responders. However, possible selection bias was reduced with the inclusion of these variables within the adjustment model. Also, patients who underwent radiotherapy in the private sector were not included but these represent less than 10% of the national radiotherapy use [38].

The main limitation of the study was that we did not have baseline PROMs (EPIC-26 and EQ-5D-5L scores) at the time of diagnosis. However, the regression analyses were adjusted for many important patient characteristics as well as for whether or not men had GI and GU procedures in the year before the start of radiotherapy. Therefore, the impact of including baseline PROMs in the models is likely to be small given that this will only lead to adjustment over and above what is already captured in our regression models.

This is in line with the results of our additional analysis. Men who received EBRT with HDR-BB had better recalled baseline urinary, sexual and bowel function than men who received EBRT only. Including these recalled baseline function scores in the regression models indicated that our study may have slightly underestimated the impact of adding HDR-BB. Furthermore, it has been shown that there is very little difference in baseline function between treatment modalities (EBRT, surgery or observation), with the exception of sexual function [39].

It is important to note in this context that EQ-5D-5L was found to be better for men who received EBRT with HDR-BB compared to men who received EBRT only. This difference, suggesting better HRQoL in men who had EBRT with HDR-BB than in men who only had EBRT, supports our interpretation that the impact of HDR-BB to EBRT on functional outcomes is small.

Although the total number of patients included was high (13,259), there were relatively small numbers of men receiving EBRT with HDR-BB (756). Only 13 HDR brachytherapy centres in England were identified which reflects that EBRT with HDR-BB is used relatively infrequently.

Conclusions

There is no evidence to suggest that EBRT with HDR-BB results in clinically worse functional outcomes or HRQoL than EBRT after a median time of 16 months. However, men who had EBRT with HDR-BB reported significantly worse urinary irritation/obstruction compared to men who had EBRT only, but results were inconclusive as to whether this difference was clinically important. Given the current state of evidence, clinicians should inform their patients receiving EBRT with HDR-BB that their urinary function may be worse in the first years after treatment.

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Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.10.019.

References

[1] Gray PJ, Zietman AL. Dose-escalated radiotherapy for prostate cancer: is the sky the limit?. JAMA Oncol 2015;1(7):883–4.

[2] Dayes IS, Parpia S, Gilbert J, Julian JA, Davis IR, Levine MN, et al. Long-term results of a randomized trial comparing iridium implant plus external beam radiation therapy with external beam radiation therapy alone in node-negative locally advanced cancer of the prostate. Int J Radiat Oncol Biol Phys 2017;99(1):90–3.

[3] Hoskin PJ, Motohashi K, Bownes P, Bryant L, Ostler P. High dose rate brachytherapy in combination with external beam radiotherapy in the radical treatment of prostate cancer: initial results of a randomised phase three trial. Radiother Oncol 2007;84(2):114–20.

[4] Hoskin PJ, Rojas AM, Bownes PJ, Lowe GJ, Ostler PJ, Bryant L. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. Radiother Oncol 2012;103(2):217–22.

[5] Hoskin PJ, Rojas AM, Ostler PJ, Hughes R, Lowe GJ, Bryant L. Quality of life after radical radiotherapy for prostate cancer: longitudinal study from a randomised trial of external beam radiotherapy alone or in combination with high dose rate brachytherapy. Clin Oncol (R Coll Radiol) 2013;25(5):321–7.

[6] Morris WJ, Tyldesley S, Rodda S, Halperin R, Pai H, McKenzie M, et al. Androgen suppression combined with elective nodal and dose escalated radiation therapy (the ASCENDE-RT Trial): An analysis of survival endpoints for a randomized trial comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. Int J Radiat Oncol Biol Phys 2017;98(2):275–85.

[7] Rodda S, Tyldesley S, Morris WJ, Keyes M, Halperin R, Pai H, et al. ASCENDE-RT: An analysis of treatment-related morbidity for a randomized trial comparing a low-dose-rate brachytherapy boost with a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. Int J Radiat Oncol Biol Phys 2017;98(2):286–95.

[8] Sathya JR, Davis IR, Julian JA, Guo Q, Daya D, Dayes IS, et al. Randomized trial comparing iridium implant plus external-beam radiation therapy with external-beam radiation therapy alone in node-negative locally advanced cancer of the prostate. J Clin Oncol 2005;23(6):1192–9.

[9] Pieters BR, de Back DZ, Koning CC, Zwinderman AH. Comparison of three radiotherapy modalities on biochemical control and overall survival for the treatment of prostate cancer: a systematic review. Radiother Oncol 2009;93(2):168–73.

[10] Kishan AU, Cook RR, Ciezki JP, Ross AE, Pomerantz MM, Nguyen PL, et al. Radical prostatectomy, external beam radiotherapy, or external beam radiotherapy with brachytherapy boost and disease progression and mortality in patients with gleason score 9–10 prostate cancer. JAMA 2018;319(9):896–905.

[11] National Institute for Health and Care Excellence (NICE). Prostate Cancer: Diagnosis and Treatment. [Available from: http://www.nice.org.uk/guidance/cg175.

[12] Spratt DE, Zumsteg ZS, Ghadjar P, Kollmeier MA, Pei X, Cohen G, et al. Comparison of high-dose (86.4 Gy) IMRT vs combined brachytherapy plus IMRT for intermediate-risk prostate cancer. BJU Int 2014;114(3):360–7.

[13] National Cancer Intelligence Network. National Cancer Data Repository. [Available from: http://www.ncin.org.uk/collecting_and_using_data/national_cancer_data_repository/.

[14] National Cancer Registration and Analysis Service. National Radiotherapy Dataset (RTDS) [Available from: http://www.ncin.org.uk/collecting_and_using_data/rtds.

[15] National Health Service. Hospital Episode Statistics [Available from: http://www.hesonline.nhs.uk.

[16] World Health Organisation. International Statistical Classification of Diseases and Related Health Problems (10th Revision). [Available from: http://www.who.int/classifications/icd/ICD10Volume2_en_2010.pdf.

[17] National Prostate Cancer Audit. Annual Report 2018: Results of the NPCA Prospective Audit in England and Wales for men diagnosed from 1 April 2016 - 31 March 20[Available from: https://www.npca.org.uk/reports/npca-annual-report-2018/.

[18] Parry MG, Sujenthiran A, Cowling TE, Charman S, Nossiter J, Aggarwal A, et al. Imputation of missing prostate cancer stage in English cancer registry data based on clinical assumptions. Cancer Epidemiol 2019;58:44–51.

[19] Szymanski KM, Wei JT, Dunn RL, Sanda MG. Development and validation of an abbreviated version of the expanded prostate cancer index composite instrument for measuring health-related quality of life among prostate cancer survivors. Urology 2010;76(5):1245–50.

[20] Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20(10):1727–36.

[21] University of Michigan. Scoring Instructions for the Expanded Prostate cancer Index Composite Short Form (EPIC-26) (2002). [Available from: https://medicine.umich.edu/sites/default/files/content/downloads/Scoring%20Instructions%20for%20the%20EPIC%2026.pdf.

[22] The EuroQol Group. EQ-5D-5L User Guide. Basic information on how to use the EQ-5D-5L instrument (2015). [Available from: http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/EQ-5D-5L_UserGuide_2015.pdf.

[23] . Noble M, McLennan D, Wilkinson K, Whitworth A, Dibben C, Barnes H. The English Indices of Deprivation 2007. [Available from: http://geoconvert.mimas.ac.uk/help/imd-2007-manual.pdf.

[24] Armitage JN, van der Meulen JH. Royal College of Surgeons Co-morbidity Consensus G. Identifying co-morbidity in surgical patients using administrative data with the Royal College of Surgeons Charlson Score. Br J Surg 2010;97(5):772–81.

[25] National Health Service. OPCS-4 Classification of Interventions and Procedures [cited 2018 8 January]. Available from: http://www.digital.nhs.uk/article/1117/Clinical-Classifications.

[26] Sujenthiran A, Nossiter J, Charman SC, Parry M, Dasgupta P, van der Meulen J, et al. National population-based study comparing treatment-related toxicity in men who received intensity modulated versus 3-dimensional conformal radical radiation therapy for prostate cancer. Int J Radiat Oncol Biol Phys 2017;99:1253–60.

[27] Parry MG, Sujenthiran A, Cowling TE, Nossiter J, Cathcart P, Clarke NW, et al. Treatment-related toxicity using prostate-only versus prostate and pelvic lymph node intensity-modulated radiation therapy: a national population-based study. J Clin Oncol 2019. Jco1802237..

[28] Nossiter J, Sujenthiran A, Cowling TE, Parry MG, Charman SC, Cathcart P, et al. Patient-reported functional outcomes after hypofractionated or conventionally fractionated radiation for prostate cancer: a national cohort study in England. J Clin Oncol 2020;38(7):744–52.

[29] Skolarus TA, Dunn RL, Sanda MG, Chang P, Greenfield TK, Litwin MS, et al. Minimally important difference for the Expanded Prostate Cancer Index Composite Short Form. Urology 2015;85(1):101–5.

[30] Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes 2007;5:70.

[31] Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials 1989;10(4):407–15.

[32] Rothmann MD, Wiens BL, Chan IS. Design and analysis of non-inferiority trials. CRC Press; 2011.

[33] National Institute for Health and Care Excellence. Prostate cancer: diagnosis and management (2019). [Available from: https://www.nice.org.uk/guidance/ng131/resources/prostate-cancer-diagnosis-and-management-pdf-66141714312133.

[34] Mohammed N, Kestin L, Ghilezan M, Krauss D, Vicini F, Brabbins D, et al. Comparison of acute and late toxicities for three modern high-dose radiation treatment techniques for localized prostate cancer. Int J Radiat Oncol Biol Phys 2012;82(1):204–12.

[35] Khor R, Duchesne G, Tai KH, Foroudi F, Chander S, Van Dyk S, et al. Direct 2-arm comparison shows benefit of high-dose-rate brachytherapy boost vs external beam radiation therapy alone for prostate cancer. Int J Radiat Oncol Biol Phys 2013;85(3):679–85.

[36] Fang FM, Wang YM, Wang CJ, Huang HY, Chiang PH. Comparison of the outcome and morbidity for localized or locally advanced prostate cancer treated by high-dose-rate brachytherapy plus external beam radiotherapy (EBRT) versus EBRT alone. Jpn J Clin Oncol 2008;38(7):474–9.

[37] Soumarova R, Homola L, Perkova H, Stursa M. Three-dimensional conformal external beam radiotherapy versus the combination of external radiotherapy with high-dose rate brachytherapy in localized carcinoma of the prostate: comparison of acute toxicity. Tumori 2007;93(1):37–44.

[38] Aggarwal A, Lewis D, Sujenthiran A, Charman SC, Sullivan R, Payne H, et al. Hospital quality factors influencing the mobility of patients for radical prostate cancer radiation therapy: a national population-based study. Int J Radiat Oncol Biol Phys 2017;99(5):1261–70.

[39] Barocas DA, Alvarez J, Resnick MJ, Koyama T, Hoffman KE, Tyson MD, et al. Association between radiation therapy, surgery, or observation for localized prostate cancer and patient-reported outcomes after 3 years. JAMA 2017;317(11):1126–40.

8 DISCUSSION

The main aim of this PhD was to use linked routinely collected hospital data to assess the use of different radiotherapy treatment strategies for men with locally advanced prostate cancer and investigate whether they have any detrimental impact on patient outcomes. The objectives were divided into three components: methodological development work, health services research and effectiveness studies.

8.1 Methodological Development Work

8.1.1 Data Completeness

Summary of Findings

An important data source for this thesis was cancer stage data from the English cancer registry. Developing and validating ways to improve the completeness of cancer stage data was therefore paramount for all further research papers. Clinical assumptions were developed based on common clinical practice to improve the ability for risk stratification. Assumptions were made based on the fact that men without high-risk disease are unlikely to have, or be investigated for, nodal or distant metastases. Similar assumptions were made for patients who had complete data for nodal status but missing data for distant metastases, given that if staging data is available for nodal disease, it is also likely that staging was performed to look for distant metastases.

Overall survival of patients with available N- or M-stage were similar to those with imputed results based on these three clinical assumptions, thus providing evidence for their validity. Using these methods, the completeness of cancer stage data, recorded in the English cancer registry between 2010 and 2013, could be

improved from 43% to 58%. Subsequent analyses in later time periods after 2014 have shown that data completeness has continued to improve after using these assumptions. The latest estimates are up to 91% complete.

Clinical, Policy and Research Implications

The main advantages of these assumptions over statistical methods is their simplicity and ease of application. The clinical assumptions impute just one value for each missing N or M variable, whereas multiple imputation produces a distribution of values (across several datasets). This means that with our clinical assumptions local hospitals can summarise and analyse their data easily without the need for statistical software or expertise. This is of particular relevance when reviewing local treatment practices and outcomes as part of clinical audit and quality improvement.

One could also use this clinical method followed by statistical imputation as a second step in order to account for the remainder. This approach may also be applicable to other cancer registries in order to improve data completeness. However, prostate cancer is unique in that full staging investigations are not always warranted, and treatment is not always required, which may limit its use in other cancer types. Specific assumptions would need to be tailored to each cancer type given the differences in their diagnostic pathways.

8.1.2 Skeletal-related Events

Summary of Findings

Prognostic or therapeutic determinants of the outcomes of prostate cancer patients often need a long follow-up period due to the natural history of the disease. Therefore, in order to report on patient survival a long follow-up is required. Markers

of disease progression are therefore attractive alternative outcomes because they occur earlier in the course of the disease and it is expected that up to 50% of men with bone metastases will experience a skeletal-related event (122). Skeletal-related events consist of high-morbidity clinical episodes and represent a substantial challenge in the management of metastatic prostate cancer (28).

Up until now it has not been possible to report disease progression when using routinely collected hospital data in England. I was able to show that using administrative hospital data and radiotherapy data it is possible to identify skeletal-related events in men with prostate cancer. Identifying skeletal-related events based on these codes provides a useful measure of cancer progression which I was able to use in subsequent treatment effectiveness work. This coding framework was applied effectively in Research Paper 7 to compare EBRT only, HDR-BB and LDR-BB groups.

Clinical, Policy and Research Implications

Given the explicit and transparent coding framework, these methods are reproducible and applicable to other national routinely collected data that use the same diagnosis codes and related procedure codes. An example of this is within a metastatic population. The treatment options for metastatic prostate cancer are rapidly developing where new novel agents (e.g. Enzalutamide) in the hormone sensitive and castrate-resistant settings are able to reduce the incidence of skeletal-related events and prolong survival (123-125). The ability to identify the occurrence of skeletal-related events in a 'real-world' national population is paramount in order to describe disease trends and assess the impact of these novel treatments. The use of routinely collected hospital data is also important for the accurate reporting of these events in trial populations. In fact, the Systemic Therapy in Advancing or Metastatic

Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial listed this as a particular limitation of their trial design and indicates that "linkage to hospital records is required to report more detailed information on skeletal-related events" (124). The linkage of trial data to routine data sources therefore allows for the accurate reporting on long term prostate cancer outcomes with less burden on the data collection teams. Equally the coding framework developed can be applied to other cancer groups to provide 'real-world', large-scale comparisons of treatment effectiveness.

8.2 Health Services Research

Summary of Findings

The centralisation of cancer services across Europe and the UK has been shown to result in differential access to treatment between hospitals (77, 78). Given the importance of radical treatment to men with locally advanced prostate cancer, it was important to see if treatment inequity had resulted from the adoption of a 'hub and spoke' model in terms of English prostate cancer services. The creation of specialist MDTs at the centre of prostate cancer service re-organisation has not led to any differences in whether men receive radical treatment based on where they are diagnosed. However, the provision of surgical services or specialist brachytherapy units at specific hospitals in England was associated with treatment selection.

The reasons underlying this finding may partly be explained by the fact that discussions within regional referral networks are focused on whether or not to offer radical treatment but the type of treatment selected is still left to those directly involved in the patient's management. More specifically, the limited regional

availability of a brachytherapy boost is likely to be preventing its selection in specific geographical areas of England.

Clinical, Policy and Research Implications

It is important that all potential options are considered when a patient is deemed fit for radical treatment. For this to happen, patient and multi-clinician input into shared decision-making is required. The effective working of multi-disciplinary teams and joint clinics (with urology and oncology input) allow for a balanced approach between surgery and radiotherapy which will be less prone to specialty bias. More importantly, patients need to be involved in these management decisions and the use of joint clinics will allow for effective and preference-sensitive care given that multiple treatment options are available.

All diagnostic hospitals of prostate cancer within England have an MDT and each MDT is part of a larger specialist MDT for complex management decisions. 41% of men diagnosed with prostate cancer have locally advanced disease (14) but only 4.4% of the men who go on to receive radiotherapy also receive a brachytherapy boost. This is surprising given that 24 of the 48 specialist MDTs in England include a radiotherapy centre that offers brachytherapy, but there are only 13 radiotherapy centres (out of 56, as of 2019) which use a brachytherapy boost regularly.

Despite emerging evidence of better biochemical control of EBRT-BB compared to EBRT only, NICE guidelines currently do not recommend a brachytherapy boost as first-line management for intermediate- or high-risk prostate cancer and only recommend for its consideration. Until a survival advantage has been shown compared to radiotherapy in a randomised trial, it is unlikely for guidelines to change in favour of

a brachytherapy boost and therefore increasing its provision locally is difficult to justify to hospital commissioners. PIVOTALboost is currently recruiting and will provide a definitive answer with respect to HDR-BB versus EBRT only. If preferential with respect to a brachytherapy boost, results will encourage more radiotherapy centres to provide these services as well as widening service access (73).

With evidence of improved biochemical control over EBRT only, the regional disparity shown in treatment access could be contributing to worse cancer outcomes in regions without a local centre performing a brachytherapy boost. Low availability and the lack of co-ordination within and between specialist MDTs are likely to be contributing to this. Whilst the results of PIVOTALboost are awaited, it is important that the option of a brachytherapy boost, if thought to be beneficial, is available to patients who are not diagnosed within a given regional referral network. This can only be achieved by the expansion of brachytherapy services and the establishment of inter-region referral pathways. Effective co-ordination between radiotherapy centres will need to be developed to limit access issues and potential solutions may require video consultations and pathway navigators for patients diagnosed in areas of the country which are currently out of reach of a brachytherapy centre.

It remains difficult to see how oncologists, who do not routinely offer a brachytherapy boost, would discuss this option or refer patients onto a centre which does. A national consensus in how to handle this clinical scenario is therefore warranted. National clinical audit will also be important to ensure that appropriate clinical benchmarking is taking place with respect to treatment outcomes.

8.3 Effectiveness Studies

8.3.1 Pelvic Lymph Node Irradiation

Summary of Findings

No previous studies have compared the toxicity and functional outcomes of PO-EBRT to PPLN-EBRT for men with locally advanced prostate cancer receiving exclusively IMRT. Two of the publications included within this PhD (Research Papers 4 and 5) showed no difference in toxicity between these two groups. A key conclusion from this thesis is therefore that pelvic lymph node irradiation should be at least considered for the treatment of men with locally advanced prostate cancer, given that it does not cause worse toxicity.

Clinical, Policy and Research Implications

These findings are particularly relevant given the recent evidence suggesting that the pattern of relapse after radiotherapy to the prostate is more nodal-centric than previously thought, emphasising the importance of extending the treatment field to include the pelvic lymph nodes (126). In addition, with the advent of molecular imaging, men can be more appropriately assessed with respect to lymph node involvement to identify truly non-metastatic, locally advanced prostate cancer. This will improve decision making with regards to the inclusion of pelvic lymph nodes within the radiation field as part of primary treatment (127).

Pelvic lymph node disease is also a common site of failure in men receiving radiotherapy to the prostate bed after radical prostatectomy which also suggests that pelvic lymph node irradiation is beneficial in the adjuvant and salvage settings (128). Further work is warranted with respect to the treatment-related toxicity after post-

prostatectomy radiotherapy and the additional impact, if any, of irradiating the pelvic lymph nodes.

Further advances are also being made in this area. Phase II trials have already confirmed the tolerability of higher radiation doses and hypofractionation in PPLN-IMRT (54, 129). More importantly, there are three RCTs being undertaken using IMRT which will confirm the definitive role of pelvic lymph node irradiation in terms of cancer control, but these studies do not have sufficient statistical power to compare toxicity rates due to the low incidence of toxicities (44, 45, 130). Observational research within this PhD can provide important information to clinicians with respect to toxicity despite its non-randomised nature. The clinical allocation of patients to treatment groups is unlikely to be related to the occurrence of toxicity, given that these are often unintended and unpredictable. Therefore, comparisons with respect to toxicity are still reliable even in the absence of randomisation (131).

8.3.2 Brachytherapy Boost

Summary of Findings

Research Papers 6 and 7 demonstrated that adding a brachytherapy boost is associated with increased radiotherapy-related toxicity for men with prostate cancer. Our findings would suggest that, if a brachytherapy boost is considered, HDR-BB is preferable over LDR-BB given its lower rate of GI toxicity. Both LDR-BB and HDR-BB had significantly worse urinary irritation/obstruction scores than EBRT only but only the difference between LDR-BB and EBRT only groups definitively met the threshold to be clinically important. Our findings also suggest that HDR-BB may improve cancer outcomes compared to EBRT only.

Clinical, Policy and Research Implications

It is still unknown which type of brachytherapy boost is most beneficial in terms of cancer survival and a definitive RCT will be required to answer this question. PIVOTALboost is currently recruiting and will at least provide an answer with respect to HDR-BB versus EBRT only (73). Until these RCTs have been performed, the toxicity results from this thesis can aid the appropriate counselling of patients when making decisions about radiotherapy for prostate cancer. Any higher GU toxicity needs to be managed relative to the oncological benefit. Further to this, it is important that the findings with respect to GI toxicity following LDR-BB are not ignored and should encourage further national conversation within the radiation oncology community to discuss the long-term future of LDR-BB and whether a transition towards HDR-BB is preferable. Currently there are two centres within England which treat the majority of the LDR-BB cases and these results warrant a process of prospective assessment to ascertain if any learning curve effect is leading to the current observed treatment-related toxicity.

It is also important to consider these results within the general population as older men were much less likely to receive a brachytherapy boost than younger men. Given an aging population and the fact that most men are diagnosed with prostate cancer in later life, knowledge of toxicity in older patients will help to guide treatment decisions. Differential toxicity profiles according to age were not explored within this thesis and these comparisons are required in future research. This is particularly important given that elderly patients are often not included within modern RCT inclusion criteria (13, 132). Encouragingly though there is no upper age limit specified in the study inclusion criteria of PIVOTALboost and men are only excluded if they have

a life expectancy of less than 5 years (73). In the mean-time, 'real-world' data can fill an important knowledge gap in terms of treatment-related toxicity for elderly patients.

8.3.3 Other Considerations

The novelty of this work is that it provides two measures of toxicity to compare different treatments for prostate cancer. Toxicity was measured according to the need for a procedural intervention and the occurrence of diagnostic codes compatible with a recognised post radiotherapy complication, as identified through administrative hospital data, and using results from the NPCA patient-reported outcome survey, the agreement of which enhances the robustness of the conclusions. There are minimal reports of functional outcomes following either pelvic lymph node irradiation or a brachytherapy boost, and PROMs are therefore providing essential information for the evaluation of the safety of radical prostate cancer treatment (29, 30). These results will provide clinicians with reliable information with respect to treatment-related toxicity but from the perspective of the patient.

The work contained within this thesis is embedded within the NPCA which has the primary aim of service evaluation and quality improvement (14). As such the PROMs were collected as part of this process without the ability to collect baseline results. This has the potential to cause residual confounding if treatment groups are not directly comparable at baseline. A particular example was that men receiving EBRT-BB were younger, healthier, more affluent and had better recalled baseline function than men receiving EBRT only. This also raises a further issue with respect to the accuracy that patients can recall their function 18 months previously (a factor that is likely to be affected by age, among others). Further research should aim to investigate this complexity and whether having baseline PROMs has any impact on

PROMs at subsequent time points. Showing that this residual confounding can be accounted for based on other baseline factors alone would be important to know especially if PROMs are to be used for national audit purposes.

The methods of measuring treatment-related toxicity described in this thesis can also be applied to national clinical audit and quality improvement work. At present, GI and GU toxicity measures are used to compare hospital providers of surgery and radiotherapy services in prostate cancer as part of the NPCA (14). This can now be widened to include multiple radiotherapy treatment strategies as they become more increasingly used. Trends can also be observed across the country as improvements in radiotherapy delivery are made.

8.4 Strengths & Limitations

8.4.1 Routinely Collected Hospital Data

The key strength of using cancer registry data is the national coverage. English cancer registry data includes all new diagnoses of prostate cancer and includes all NHS hospitals in England. This ensures that the findings are nationally generalisable (110). The population-based studies included within this PhD were therefore able to include large volumes of patients which ensured that the studies were adequately powered.

The main limitation of cancer registry data is the data completeness and this was partially overcome based on the clinical assumptions developed in Research Paper 1. Residual missing data, however, prevented complete risk stratification. This is particularly relevant to these analyses given that excluding men with unknown risk has the potential to introduce selection bias if this group contained men with locally advanced disease.

This risk should be considered low given that these particular men all received radical local treatment. As such, it is likely they would have undergone appropriate staging investigations to rule out any distant metastases and less likely to have missing staging data. This is supported by a study of Swedish cancer registry data which showed that men with incomplete staging tended to be of low- or intermediate-risk (133). Further to this, I would expect any selection bias caused by exclusion of these men to be minimal given the clinical assumptions could account for some missing cancer stage data. The remainder is more likely to be missing at random and unlikely to bias the results.

The use of the RTDS and HES was used to identify the treatments that men received. The accuracy of these data has been shown to be high when compared to clinical notes and is sufficiently robust to support its use in research (108). Therefore, it can be assumed that if an OPCS-4 code is present in the RTDS or HES then that procedure was undertaken. This ensures that the allocated treatment is reliable. I would expect that any misclassification due to coding errors would mostly be non-differential and would result in little bias in any study comparisons. An example of this is when patients are diagnosed within the NHS, and identified through the cancer registry, but treated in the private sector. However, it is expected that less than 10% of English patients undergoing treatment for prostate cancer are treated privately. Any misclassification would therefore be minimal (107).

A further limitation of the RTDS is that it is a relatively new data source (initiated in 2009) and so follow-up beyond 5 years is only available for a limited number of men. This is particularly important given that skeletal-related events and prostate cancer-specific mortality are infrequent within the first five years of radical treatment. As

these data mature, comparisons with respect to late toxicities (including second malignancies) and cancer outcomes (including 5 and 10 year overall survival) will become possible.

HES was not only used for treatment allocation but also to measure toxicity. A major strength of these outcome measures is that they were not based on clinician reporting and were purely dependent on coding within an administrative hospital database (6, 99). They were also developed to include both diagnostic and procedure codes which maximises their specificity and minimises the risk of misclassification bias. There is a possible risk of missing diagnostic or procedure codes for those men who did have evident toxicity but, as mentioned earlier, the accuracy of these codes is high and up to 90% as of 2010 (107). In addition, in the unlikely event of misclassification it is likely to be non-differential between treatment groups as this coding is not dependent on treatment allocation.

The main limitation of using observational data for effectiveness research is the lack of randomisation which carries the risk of confounding. Differences between treatment groups, beyond that of the treatment received, could explain the study results. For example, the men receiving pelvic lymph node irradiation or a brachytherapy boost tended to be younger, healthier and more affluent than the comparator groups. To mitigate for this, regression analyses were used to adjust all comparisons for a number of important patient characteristics as well as for whether or not men had GI and GU procedures in the year before treatment. Men with worse baseline function are more likely to have undergone diagnostic investigations and so a measure of prior procedures can act as a proxy measure for baseline GI and GU function. The selected GI and GU procedure codes in HES records of hospital

admissions were based on codes for lower GI endoscopy or procedures of the lower urinary tract (6).

Although our regression analyses included the relevant confounders that were available in our data, residual confounding still remained as a consequence of any potential confounders which were not included or from confounders that were incompletely captured. All included men had undergone radiotherapy and so I would expect a reasonable degree of similarity between the treatment groups but results have been interpreted in light of this limitation.

A validated method to identify co-morbidity data in HES was also used which provided reliable identification of co-morbidity (RCS Charlson score) (100). However, given that toxicity is closely associated with age and comorbidity, a clinical tool for measuring comorbidities, not reliant on administrative data (i.e. the Adult Co-Morbidity Evaluation [ACE-27]) would provide a better measure of baseline comorbidity (134).

8.4.2 Patient-reported Outcome Measures

PROMs are an increasingly important information source regarding the impact of different treatments on individual patients. PROMs are able to provide a more comprehensive assessment of patient outcomes than clinician-reported outcome measures, typically treatment-related toxicity and patient satisfaction (135). More broadly, national audits are using PROMs to assess population-based public health burdens based on patient experiences and health outcomes. For example, the NPCA of England and Wales has collected surveys on over 45,000 men to better understand the impact of prostate cancer, its treatments and side effects (109).

The patient survey used was a comprehensive validated instrument for collecting PROMs which included EPIC-26 and EQ-5D-5L to accurately measure functional outcomes and health-related quality of life. This provided a wider view of toxicity following prostate cancer treatment. Furthermore, the agreement between both toxicity measures in Research Paper 7 is encouraging and enhances the robustness of our conclusions.

The main strength of the patient surveys I used was the high questionnaire response rate which reduces the risk of any potential selection bias from non-responders. Response rates were surprisingly high given response rates from other patient surveys (136). For Research Papers 5, 6 and 7, responders tended to be older, of white ethnicity, from a less socially deprived area and had fewer comorbidities than non-responders but any possible selection bias was reduced with the inclusion of these variables within the adjustment model.

The main limitation of our PROMs survey was that we did not have a measure of baseline PROMs at the time of diagnosis. However, as previously mentioned, the regression analyses were adjusted for many important patient characteristics as well as for whether or not men had GI and GU procedures in the year before treatment. Given these adjustment variables, the impact of not including baseline PROMs in the models is likely to be reduced given that this will only lead to adjustment over and above what is already captured in our regression models. Furthermore, Barocas et al. (121) showed that there is very little difference in baseline function between different treatment modalities (radiotherapy, surgery or observation), with the exception of sexual function (121). This said, it is important to highlight that a brachytherapy boost is only considered for men with good urinary function and so this treatment group is

likely to have substantially better baseline urinary function than men receiving EBRT only. Therefore any 'worse' function following a brachytherapy boost is likely to be under-estimated and this should be taken into account when interpreting these findings.

9 CONCLUSIONS

Improvements of methods for handling missing data and identifying cancer progression can overcome some of the limitations inherent to using routinely collected hospital data. Methodological development work is vital so that this type of data can be used for future health services research and effectiveness studies.

Routinely collected hospital data can be used to compare different radiotherapy treatment strategies with respect to toxicity and cancer outcomes. The agreement between these toxicity measures and patient-reported outcomes enhances the robustness of these methods and their ability to guide treatment decisions.

Additional pelvic lymph node irradiation is not associated with worse side effects and should be considered in locally advanced prostate cancer. In addition, if a brachytherapy boost is considered, a high-dose rate is preferable over a low-dose rate given its lower rate of gastrointestinal toxicity and its better cancer control compared to radiotherapy only. Treatment selection is also affected by the local provision of specialist services and, taken together, these results can be used to help improve service organisation especially with regards to a brachytherapy boost.

10 REFERENCES

1. Cancer Research UK. Prostate Cancer Statistics; Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer#heading-Two (accessed 27 September, 2017).

2. Makarov DV, Trock BJ, Humphreys EB, Mangold LA, Walsh PC, Epstein JI, et al. Updated nomogram to predict pathologic stage of prostate cancer given prostate-specific antigen level, clinical stage, and biopsy Gleason score (Partin tables) based on cases from 2000 to 2005. *Urology*. 2007;69(6):1095-101.

3. National Prostate Cancer Audit. Third Year Annual Report - Results of the NPCA Prospective Audit and Patient Survey (2016). Available at: https://www.npca.org.uk/content/uploads/2017/11/NPCA-2016-Annual-Report-Final_131216.pdf (accessed February 16, 2018).

4. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA*. 1998;280(11):969-74.

5. Nicholls SG, Langan SM, Benchimol EI. Routinely collected data: the importance of high-quality diagnostic coding to research. *Cmaj*. 2017;189(33):E1054-e5.

6. Sujenthiran A, Nossiter J, Charman SC, Parry M, Dasgupta P, van der Meulen J, et al. National Population-Based Study Comparing Treatment-Related Toxicity in Men Who Received Intensity Modulated Versus 3-Dimensional Conformal Radical Radiation Therapy for Prostate Cancer. *Int J Radiat Oncol Biol Phys*. 2017;99:1253-60.

7. Sujenthiran A, Nossiter J, Charman SC, Parry M, Dasgupta P, van der Meulen J, et al. National Population-Based Study Comparing Treatment-Related Toxicity in Men

Who Received Intensity Modulated Versus 3-Dimensional Conformal Radical Radiation Therapy for Prostate Cancer. *Int J Radiat Oncol Biol Phys*. 2017.

8. Crandley EF, Hegarty SE, Hyslop T, Wilson DD, Dicker AP, Showalter TN. Treatment-related complications of radiation therapy after radical prostatectomy: comparative effectiveness of intensity-modulated versus conformal radiation therapy. *Cancer Med*. 2014;3(2):397-405.

9. Goldin GH, Sheets NC, Meyer AM, Kuo TM, Wu Y, Sturmer T, et al. Comparative effectiveness of intensity-modulated radiotherapy and conventional conformal radiotherapy in the treatment of prostate cancer after radical prostatectomy. *JAMA Intern Med*. 2013;173(12):1136-43.

10. Sheets NC, Goldin GH, Meyer AM, Wu Y, Chang Y, Sturmer T, et al. Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. *Jama*. 2012;307(15):1611-20.

11. Aizer AA, Gu X, Chen MH, Choueiri TK, Martin NE, Efstathiou JA, et al. Cost implications and complications of overtreatment of low-risk prostate cancer in the United States. *J Natl Compr Canc Netw*. 2015;13(1):61-8.

12. Rothwell PM. Factors that can affect the external validity of randomised controlled trials. *PLoS Clin Trials*. 2006;1(1):e9.

13. Warde P, Mason M, Ding K, Kirkbride P, Brundage M, Cowan R, et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. *Lancet*. 2011;378(9809):2104-11.

14. National Prostate Cancer Audit. Annual Report 2019: Results of the NPCA Prospective Audit in England and Wales for men diagnosed from 1 April 2017 - 31

March 2018. Available at: https://www.npca.org.uk/reports/npca-annual-report-2019/ (accessed January 2020, 2020).

15. Healthcare Quality Improvement Partnership. Clinical Outcomes Publication Available at: https://www.hqip.org.uk/national-programmes/clinical-outcomes-publication/#.X2OVS4vTXIU (accessed September 17, 2020).

16. Sogaard M, Olsen M. Quality of cancer registry data: completeness of TNM staging and potential implications. *Clin Epidemiol*. 2012;4 Suppl 2:1-3.

17. Nur U, Shack LG, Rachet B, Carpenter JR, Coleman MP. Modelling relative survival in the presence of incomplete data: a tutorial. *Int J Epidemiol*. 2010;39(1):118-28.

18. Gandaglia G, Bray F, Cooperberg MR, Karnes RJ, Leveridge MJ, Moretti K, et al. Prostate Cancer Registries: Current Status and Future Directions. *Eur Urol*. 2015.

19. Giordano SH, Kuo YF, Duan Z, Hortobagyi GN, Freeman J, Goodwin JS. Limits of observational data in determining outcomes from cancer therapy. *Cancer*. 2008;112(11):2456-66.

20. Penson DF, Albertsen PC. Lessons learnt about early prostate cancer from large scale databases: population-based pearls of wisdom. *Surg Oncol*. 2002;11(1-2):3-11.

21. Luo Q, Yu XQ, Cooke-Yarborough C, Smith DP, O'Connell DL. Characteristics of cases with unknown stage prostate cancer in a population-based cancer registry. *Cancer Epidemiol*. 2013;37(6):813-9.

22. Nguyen-Nielsen M, Froslev T, Friis S, Borre M, Harving N, Sogaard M. Completeness of prostate cancer staging in the Danish Cancer Registry, 2004-2009. *Clin Epidemiol*. 2012;4 Suppl 2:17-23.

23. Eisemann N, Waldmann A, Katalinic A. Imputation of missing values of tumour stage in population-based cancer registration. *BMC Med Res Methodol*. 2011;11:129.

24. Marshall A, Altman DG, Royston P, Holder RL. Comparison of techniques for handling missing covariate data within prognostic modelling studies: a simulation study. *BMC Med Res Methodol*. 2010;10:7.

25. Redaniel MT, Laudico A, Mirasol-Lumague MR, Gondos A, Uy G, Brenner H. Inter-country and ethnic variation in colorectal cancer survival: comparisons between a Philippine population, Filipino-Americans and Caucasians. *BMC Cancer*. 2010;10:100.

26. Luo Q, Egger S, Yu XQ, Smith DP, O'Connell DL. Validity of using multiple imputation for "unknown" stage at diagnosis in population-based cancer registry data. *PLoS One*. 2017;12(6):e0180033.

27. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338:b2393.

28. McDougall JA, Bansal A, Goulart BH, McCune JS, Karnopp A, Fedorenko C, et al. The Clinical and Economic Impacts of Skeletal-Related Events Among Medicare Enrollees With Prostate Cancer Metastatic to Bone. *Oncologist*. 2016;21(3):320-6.

29. Hussain A, Aly A, Daniel Mullins C, Qian Y, Arellano J, Onukwugha E. Risk of skeletal related events among elderly prostate cancer patients by site of metastasis at diagnosis. *Cancer Med*. 2016;5(11):3300-9.

30. Sathiakumar N, Delzell E, Morrisey MA, Falkson C, Yong M, Chia V, et al. Mortality following bone metastasis and skeletal-related events among men with prostate cancer: a population-based analysis of US Medicare beneficiaries, 1999-2006. *Prostate Cancer Prostatic Dis*. 2011;14(2):177-83.

31. Norgaard M, Jensen AO, Jacobsen JB, Cetin K, Fryzek JP, Sorensen HT. Skeletal related events, bone metastasis and survival of prostate cancer: a population based cohort study in Denmark (1999 to 2007). *J Urol*. 2010;184(1):162-7.

32. Aly A, Onukwugha E, Woods C, Mullins CD, Kwok Y, Qian Y, et al. Measurement of skeletal related events in SEER-Medicare: a comparison of claims-based methods. *BMC Med Res Methodol*. 2015;15:65.

33. Hagiwara M, Delea TE, Saville MW, Chung K. Healthcare utilization and costs associated with skeletal-related events in prostate cancer patients with bone metastases. *Prostate Cancer Prostatic Dis*. 2013;16(1):23-7.

34. European Association of Urology. Guidelines on Prostate Cancer (2016) Available at: http://uroweb.org/wp-content/uploads/EAU-Guidelines-Prostate-Cancer-2016.pdf (accessed February 16, 2018).

35. Locally advanced prostate cancer: effective treatments, but many adverse effects. *Prescrire Int*. 2013;22(134):18-20, 2-3.

36. Gilbert A, Ziegler L, Martland M, Davidson S, Efficace F, Sebag-Montefiore D, et al. Systematic Review of Radiation Therapy Toxicity Reporting in Randomized Controlled Trials of Rectal Cancer: A Comparison of Patient-Reported Outcomes and Clinician Toxicity Reporting. *Int J Radiat Oncol Biol Phys*. 2015;92(3):555-67.

37. National Institute for Health and Care Excellence (NICE). Prostate Cancer: Diagnosis and Treatment. Available at: http://www.nice.org.uk/guidance/cg175 (accessed 8 January, 2018).

38. Roach M, 3rd, Marquez C, Yuo HS, Narayan P, Coleman L, Nseyo UO, et al. Predicting the risk of lymph node involvement using the pre-treatment prostate specific antigen and Gleason score in men with clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 1994;28(1):33-7.

39. Aizer AA, Yu JB, McKeon AM, Decker RH, Colberg JW, Peschel RE. Whole pelvic radiotherapy versus prostate only radiotherapy in the management of locally advanced

or aggressive prostate adenocarcinoma. *Int J Radiat Oncol Biol Phys*. 2009;75(5):1344-9.

40. Asbell SO, Krall JM, Pilepich MV, Baerwald H, Sause WT, Hanks GE, et al. Elective pelvic irradiation in stage A2, B carcinoma of the prostate: analysis of RTOG 77-06. *Int J Radiat Oncol Biol Phys*. 1988;15(6):1307-16.

41. Lawton CA, DeSilvio M, Roach M, 3rd, Uhl V, Kirsch R, Seider M, et al. An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. *Int J Radiat Oncol Biol Phys*. 2007;69(3):646-55.

42. Pan CC, Kim KY, Taylor JM, McLaughlin PW, Sandler HM. Influence of 3D-CRT pelvic irradiation on outcome in prostate cancer treated with external beam radiotherapy. *Int J Radiat Oncol Biol Phys*. 2002;53(5):1139-45.

43. Pommier P, Chabaud S, Lagrange JL, Richaud P, Lesaunier F, Le Prise E, et al. Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Preliminary results of GETUG-01. *J Clin Oncol*. 2007;25(34):5366-73.

44. National Institutes of Health. A Study of Prostate and pelvIs Versus prOsTate Alone Treatment for Locally Advanced Prostate Cancer (PIVOTAL) Available at: http://clinicaltrials.gov/ct2/show/NCT01685190 (accessed March 20, 2018).

45. RTOG Foundation. RTOG 0924 Protocol Information Available at: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0924 (accessed March 20, 2018).

46. Lilleby W, Stensvold A, Dahl AA. Adding intensity-modulated radiotherapy to the pelvis does not worsen the adverse effect profiles compared to limited field

radiotherapy in men with prostate cancer at 12-month follow-up. *Acta Oncol*. 2014;53(10):1380-9.

47. Mantini G, Tagliaferri L, Mattiucci GC, Balducci M, Frascino V, Dinapoli N, et al. Effect of whole pelvic radiotherapy for patients with locally advanced prostate cancer treated with radiotherapy and long-term androgen deprivation therapy. *Int J Radiat Oncol Biol Phys*. 2011;81(5):e721-6.

48. Pinkawa M, Piroth MD, Holy R, Fischedick K, Klotz J, Szekely-Orban D, et al. Quality of life after whole pelvic versus prostate-only external beam radiotherapy for prostate cancer: a matched-pair comparison. *Int J Radiat Oncol Biol Phys*. 2011;81(1):23-8.

49. Roach M, 3rd, DeSilvio M, Valicenti R, Grignon D, Asbell SO, Lawton C, et al. Whole-pelvis, "mini-pelvis," or prostate-only external beam radiotherapy after neoadjuvant and concurrent hormonal therapy in patients treated in the Radiation Therapy Oncology Group 9413 trial. *Int J Radiat Oncol Biol Phys*. 2006;66(3):647-53.

50. National Prostate Cancer Audit. Annual Report 2017: Results of the NPCA Prospective Audit in England and Wales for men diagnosed from 1 April 2015 - 31 March 2016 (2017). Available at: http://www.npca.org.uk/content/uploads/2017/11/NPCA-2017-Annual-Report_final_211117.pdf (accessed Spetember 9, 2018).

51. Ganswindt U, Paulsen F, Corvin S, Hundt I, Alber M, Frey B, et al. Optimized coverage of high-risk adjuvant lymph node areas in prostate cancer using a sentinel node-based, intensity-modulated radiation therapy technique. *Int J Radiat Oncol Biol Phys*. 2007;67(2):347-55.

52. Habl G, Katayama S, Uhl M, Kessel KA, Edler L, Debus J, et al. Helical intensity-modulated radiotherapy of the pelvic lymph nodes with a simultaneous integrated boost to the prostate--first results of the PLATIN 1 trial. *BMC Cancer*. 2015;15:868.

53. Joo JH, Kim YJ, Kim YS, Choi EK, Kim JH, Lee SW, et al. Whole pelvic intensity-modulated radiotherapy for high-risk prostate cancer: a preliminary report. *Radiat Oncol J*. 2013;31(4):199-205.

54. Reis Ferreira M, Khan A, Thomas K, Truelove L, McNair H, Gao A, et al. Phase 1/2 Dose-Escalation Study of the Use of Intensity Modulated Radiation Therapy to Treat the Prostate and Pelvic Nodes in Patients With Prostate Cancer. *Int J Radiat Oncol Biol Phys*. 2017;99(5):1234-42.

55. Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol*. 2016;17(8):1047-60.

56. Holch P, Henry AM, Davidson S, Gilbert A, Routledge J, Shearsmith L, et al. Acute and Late Adverse Events Associated With Radical Radiation Therapy Prostate Cancer Treatment: A Systematic Review of Clinician and Patient Toxicity Reporting in Randomized Controlled Trials. *Int J Radiat Oncol Biol Phys*. 2017;97(3):495-510.

57. Wang Y, Sankreacha R, Al-Hebshi A, Loblaw A, Morton G. Comparative study of dosimetry between high-dose-rate and permanent prostate implant brachytherapies in patients with prostate adenocarcinoma. *Brachytherapy*. 2006;5(4):251-5.

58. Dayes IS, Parpia S, Gilbert J, Julian JA, Davis IR, Levine MN, et al. Long-Term Results of a Randomized Trial Comparing Iridium Implant Plus External Beam Radiation Therapy With External Beam Radiation Therapy Alone in Node-Negative Locally Advanced Cancer of the Prostate. *Int J Radiat Oncol Biol Phys*. 2017;99(1):90-3.

59. Hoskin PJ, Motohashi K, Bownes P, Bryant L, Ostler P. High dose rate brachytherapy in combination with external beam radiotherapy in the radical treatment of prostate cancer: initial results of a randomised phase three trial. *Radiother Oncol*. 2007;84(2):114-20.

60. Hoskin PJ, Rojas AM, Bownes PJ, Lowe GJ, Ostler PJ, Bryant L. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. *Radiother Oncol*. 2012;103(2):217-22.

61. Sathya JR, Davis IR, Julian JA, Guo Q, Daya D, Dayes IS, et al. Randomized trial comparing iridium implant plus external-beam radiation therapy with external-beam radiation therapy alone in node-negative locally advanced cancer of the prostate. *J Clin Oncol*. 2005;23(6):1192-9.

62. Morris WJ, Tyldesley S, Rodda S, Halperin R, Pai H, McKenzie M, et al. Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT Trial): An Analysis of Survival Endpoints for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost to a Dose-Escalated External Beam Boost for High- and Intermediate-risk Prostate Cancer. *Int J Radiat Oncol Biol Phys*. 2017;98(2):275-85.

63. Rodda S, Tyldesley S, Morris WJ, Keyes M, Halperin R, Pai H, et al. ASCENDE-RT: An Analysis of Treatment-Related Morbidity for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost with a Dose-Escalated External Beam Boost for High- and Intermediate-Risk Prostate Cancer. *Int J Radiat Oncol Biol Phys*. 2017;98(2):286-95.

64. Pieters BR, de Back DZ, Koning CC, Zwinderman AH. Comparison of three radiotherapy modalities on biochemical control and overall survival for the treatment of prostate cancer: a systematic review. *Radiother Oncol*. 2009;93(2):168-73.

65. Kishan AU, Cook RR, Ciezki JP, Ross AE, Pomerantz MM, Nguyen PL, et al. Radical Prostatectomy, External Beam Radiotherapy, or External Beam Radiotherapy With Brachytherapy Boost and Disease Progression and Mortality in Patients With Gleason Score 9-10 Prostate Cancer. *JAMA*. 2018;319(9):896-905.

66. Spratt DE, Zumsteg ZS, Ghadjar P, Kollmeier MA, Pei X, Cohen G, et al. Comparison of high-dose (86.4 Gy) IMRT vs combined brachytherapy plus IMRT for intermediate-risk prostate cancer. *BJU Int*. 2014;114(3):360-7.

67. Hoskin PJ, Rojas AM, Ostler PJ, Hughes R, Lowe GJ, Bryant L. Quality of life after radical radiotherapy for prostate cancer: longitudinal study from a randomised trial of external beam radiotherapy alone or in combination with high dose rate brachytherapy. *Clin Oncol (R Coll Radiol)*. 2013;25(5):321-7.

68. Slevin F, Rodda SL, Bownes P, Murray L, Bottomley D, Wilkinson C, et al. A comparison of outcomes for patients with intermediate and high risk prostate cancer treated with low dose rate and high dose rate brachytherapy in combination with external beam radiotherapy. *Clin Transl Radiat Oncol*. 2020;20:1-8.

69. Mohammed N, Kestin L, Ghilezan M, Krauss D, Vicini F, Brabbins D, et al. Comparison of acute and late toxicities for three modern high-dose radiation treatment techniques for localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2012;82(1):204-12.

70. Khor R, Duchesne G, Tai KH, Foroudi F, Chander S, Van Dyk S, et al. Direct 2-arm comparison shows benefit of high-dose-rate brachytherapy boost vs external beam radiation therapy alone for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2013;85(3):679-85.

71. Fang FM, Wang YM, Wang CJ, Huang HY, Chiang PH. Comparison of the outcome and morbidity for localized or locally advanced prostate cancer treated by

high-dose-rate brachytherapy plus external beam radiotherapy (EBRT) versus EBRT alone. *Jpn J Clin Oncol*. 2008;38(7):474-9.

72. Soumarova R, Homola L, Perkova H, Stursa M. Three-dimensional conformal external beam radiotherapy versus the combination of external radiotherapy with high-dose rate brachytherapy in localized carcinoma of the prostate: comparison of acute toxicity. *Tumori*. 2007;93(1):37-44.

73. The Institute of Cancer Research. PIVOTALboost Available at: https://d1ijoxngr27nfi.cloudfront.net/docs/default-source/default-document-library/pivotalboost_protocol__v5-0_24-05-19.pdf?sfvrsn=c8f22369_0 (accessed

74. National Institute for Clinical Excellence. Guidance on cancer services: improving outcomes in urological cancers (2002) Available at: http://www.nice.org.uk/guidance/csg2/resources/improving-outcomes-in-urological-cancers-pdf-773372413 (accessed February 16, 2018).

75. Birkmeyer JD, Siewers AE, Finlayson EV, Stukel TA, Lucas FL, Batista I, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med*. 2002;346(15):1128-37.

76. Aggarwal A, Nossiter J, Cathcart P, van der Meulen J, Rashbass J, Clarke N, et al. Organisation of Prostate Cancer Services in the English National Health Service. *Clin Oncol (R Coll Radiol)*. 2016;28(8):482-9.

77. Khakwani A, Rich AL, Powell HA, Tata LJ, Stanley RA, Baldwin DR, et al. The impact of the 'hub and spoke' model of care for lung cancer and equitable access to surgery. *Thorax*. 2015;70(2):146-51.

78. Vallance AE, vanderMeulen J, Kuryba A, Botterill ID, Hill J, Jayne DG, et al. Impact of hepatobiliary service centralization on treatment and outcomes in patients with colorectal cancer and liver metastases. *Br J Surg*. 2017;104(7):918-25.

79. Henson KE, Elliss-Brookes L, Coupland VH, Payne E, Vernon S, Rous B, et al. Data Resource Profile: National Cancer Registration Dataset in England. *Int J Epidemiol*. 2020;49(1):16-h.

80. Szymanski KM, Wei JT, Dunn RL, Sanda MG. Development and validation of an abbreviated version of the expanded prostate cancer index composite instrument for measuring health-related quality of life among prostate cancer survivors. *Urology*. 2010;76(5):1245-50.

81. Schmidt S, Garin O, Pardo Y, Valderas JM, Alonso J, Rebollo P, et al. Assessing quality of life in patients with prostate cancer: a systematic and standardized comparison of available instruments. *Qual Life Res*. 2014;23(8):2169-81.

82. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20(10):1727-36.

83. National Cancer Registration and Analysis Service. National Radiotherapy Dataset (RTDS) Available at: http://www.ncin.org.uk/collecting_and_using_data/rtds (accessed December 11, 2017).

84. Herbert A, Wijlaars L, Zylbersztejn A, Cromwell D, Hardelid P. Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). *Int J Epidemiol*. 2017;46(4):1093-i.

85. Sujenthiran A, Nossiter J, Parry M, Charman SC, Aggarwal A, Payne H, et al. National cohort study comparing severe medium-term urinary complications following radical prostatectomy: robot-assisted versus laparoscopic versus retropubic open radical prostatectomy. *BJU Int*. 2017.

86. National Institutes of Health NCI. Common Terminology Criteria for Adverse Events (CTCAE) Available at: http://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (accessed January 8, 2018).

87. Gray PJ, Zietman AL. Dose-Escalated Radiotherapy for Prostate Cancer: Is the Sky the Limit? *JAMA Oncol*. 2015;1(7):883-4.

88. Deutsch I, Zelefsky MJ, Zhang Z, Mo Q, Zaider M, Cohen G, et al. Comparison of PSA relapse-free survival in patients treated with ultra-high-dose IMRT versus combination HDR brachytherapy and IMRT. *Brachytherapy*. 2010;9(4):313-8.

89. Kent AR, Matheson B, Millar JL. Improved survival for patients with prostate cancer receiving high-dose-rate brachytherapy boost to EBRT compared with EBRT alone. *Brachytherapy*. 2019;18(3):313-21.

90. Wedde TB, Smastuen MC, Brabrand S, Fossa SD, Kaasa S, Tafjord G, et al. Ten-year survival after High-Dose-Rate Brachytherapy combined with External Beam Radiation Therapy in high-risk prostate cancer: A comparison with the Norwegian SPCG-7 cohort. *Radiother Oncol*. 2019;132:211-7.

91. Johnson SB, Lester-Coll NH, Kelly JR, Kann BH, Yu JB, Nath SK. Brachytherapy Boost Utilization and Survival in Unfavorable-risk Prostate Cancer. *Eur Urol*. 2017;72(5):738-44.

92. King MT, Yang DD, Muralidhar V, Mahal B, Butler S, Devlin PM, et al. A comparative analysis of overall survival between high-dose-rate and low-dose-rate brachytherapy boosts for unfavorable-risk prostate cancer. *Brachytherapy*. 2019;18(2):186-91.

93. Marina O, Gustafson GS, Kestin LL, Brabbins DS, Chen PY, Ye H, et al. Comparison of dose-escalated, image-guided radiotherapy vs. dose-escalated, high-

dose-rate brachytherapy boost in a modern cohort of intermediate-risk prostate cancer patients. *Brachytherapy*. 2014;13(1):59-67.

94. National Cancer Intelligence Network. National Cancer Data Repository. Available at: http://www.ncin.org.uk/collecting_and_using_data/national_cancer_data_repository/ (accessed December 11, 2016).

95. National Health Service. Hospital Episode Statistics Available at: http://www.hesonline.nhs.uk (accessed January 15, 2017).

96. World Health Organisation. International Statistical Classification of Diseases and Related Health Problems (10th Revision). Available at: http://www.who.int/classifications/icd/ICD10Volume2_en_2010.pdf (accessed September 28, 2017).

97. National Health Service. OPCS-4 Classification of Interventions and Procedures Available at: http://www.digital.nhs.uk/article/1117/Clinical-Classifications (accessed 8 January, 2018).

98. University of Michigan. Scoring Instructions for the Expanded Prostate cancer Index Composite Short Form (EPIC-26) (2002). Available at: https://medicine.umich.edu/sites/default/files/content/downloads/Scoring%20Instructions%20for%20the%20EPIC%2026.pdf (accessed May 14, 2019).

99. Parry MG, Cowling TE, Sujenthiran A, Nossiter J, Berry B, Cathcart P, et al. Identifying skeletal-related events for prostate cancer patients in routinely collected hospital data. *Cancer Epidemiol*. 2019;63:101628.

100. Armitage JN, van der Meulen JH. Identifying co-morbidity in surgical patients using administrative data with the Royal College of Surgeons Charlson Score. *Br J Surg*. 2010;97(5):772-81.

101. Ministry of Housing CLG. National Statistics: English indices of deprivation 2015 Available at: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015 (accessed May 26, 2020).

102. Fine JP, Gray RP. A proportional hazards model for the subdistribution of a competing risk. *Journal of the American Statistical Association*. 1999;94:496-509.

103. Skolarus TA, Dunn RL, Sanda MG, Chang P, Greenfield TK, Litwin MS, et al. Minimally important difference for the Expanded Prostate Cancer Index Composite Short Form. *Urology*. 2015;85(1):101-5.

104. Dunn OJ. Multiple comparison among means. *J Am Stat Assoc*. 1961;56:52-64.

105. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med*. 2011;30(4):377-99.

106. Morton GC, Hoskin PJ. Brachytherapy: current status and future strategies -- can high dose rate replace low dose rate and external beam radiotherapy? *Clin Oncol (R Coll Radiol)*. 2013;25(8):474-82.

107. Aggarwal A, Lewis D, Sujenthiran A, Charman SC, Sullivan R, Payne H, et al. Hospital Quality Factors Influencing the Mobility of Patients for Radical Prostate Cancer Radiation Therapy: A National Population-Based Study. *Int J Radiat Oncol Biol Phys*. 2017;99(5):1261-70.

108. Burns EM, Rigby E, Mamidanna R, Bottle A, Aylin P, Ziprin P, et al. Systematic review of discharge coding accuracy. *J Public Health (Oxf)*. 2012;34(1):138-48.

109. National Prostate Cancer Audit. Annual Report 2018: Results of the NPCA Prospective Audit in England and Wales for men diagnosed from 1 April 2016 - 31 March 2017. Available at: https://www.npca.org.uk/reports/npca-annual-report-2018/ (accessed May 14, 2019).

110. Parry MG, Sujenthiran A, Cowling TE, Charman S, Nossiter J, Aggarwal A, et al. Imputation of missing prostate cancer stage in English cancer registry data based on clinical assumptions. *Cancer Epidemiol*. 2019;58:44-51.

111. The EuroQol Group. EQ-5D-5L User Guide. Basic information on how to use the EQ-5D-5L instrument (2015). Available at: http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/EQ-5D-5L_UserGuide_2015.pdf (accessed May 14, 2019).

112. Noble M, McLennan D, Wilkinson K, Whitworth A, Dibben C, Barnes H. The English Indices of Deprivation 2007. Available at: http://geoconvert.mimas.ac.uk/help/imd-2007-manual.pdf (accessed September 28, 2017).

113. Armitage JN, van der Meulen JH, Royal College of Surgeons Co-morbidity Consensus G. Identifying co-morbidity in surgical patients using administrative data with the Royal College of Surgeons Charlson Score. *Br J Surg*. 2010;97(5):772-81.

114. Parry MG, Sujenthiran A, Cowling TE, Nossiter J, Cathcart P, Clarke NW, et al. Treatment-Related Toxicity Using Prostate-Only Versus Prostate and Pelvic Lymph Node Intensity-Modulated Radiation Therapy: A National Population-Based Study. *J Clin Oncol*. 2019:Jco1802237.

115. Nossiter J, Sujenthiran A, Cowling TE, Parry MG, Charman SC, Cathcart P, et al. Patient-Reported Functional Outcomes After Hypofractionated or Conventionally Fractionated Radiation for Prostate Cancer: A National Cohort Study in England. *J Clin Oncol*. 2020;38(7):744-52.

116. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health Qual Life Outcomes*. 2007;5:70.

117. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials*. 1989;10(4):407-15.

118. Rothmann MD, Wiens BL, Chan IS. Design and analysis of non-inferiority trials: CRC Press; 2011.

119. Rothmann MD, Wiens BL, Chan ISC. Design and Analysis of Non-Inferiority Trials: Chapman and Hall/CRC; 2011.

120. National Institute for Health and Care Excellence. Prostate cancer: diagnosis and management (2019). Available at: https://www.nice.org.uk/guidance/ng131/resources/prostate-cancer-diagnosis-and-management-pdf-66141714312133 (accessed July 17, 2019).

121. Barocas DA, Alvarez J, Resnick MJ, Koyama T, Hoffman KE, Tyson MD, et al. Association Between Radiation Therapy, Surgery, or Observation for Localized Prostate Cancer and Patient-Reported Outcomes After 3 Years. *Jama*. 2017;317(11):1126-40.

122. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J Natl Cancer Inst*. 2004;96(11):879-82.

123. Dong L, Zieren RC, Xue W, de Reijke TM, Pienta KJ. Metastatic prostate cancer remains incurable, why? *Asian J Urol*. 2019;6(1):26-41.

124. James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet*. 2016;387(10024):1163-77.

125. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk

metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2019;20(5):686-700.

126. De Bruycker A, De Bleser E, Decaestecker K, Fonteyne V, Lumen N, De Visschere P, et al. Nodal Oligorecurrent Prostate Cancer: Anatomic Pattern of Possible Treatment Failure in Relation to Elective Surgical and Radiotherapy Treatment Templates. *Eur Urol*. 2018.

127. Abecassis JP, Ghazzar N, Peyromaure M, Giraud P. Prostate imaging: Contribution of PET PSMA and MRI. *Cancer Radiother*. 2020;24(5):423-8.

128. Brand DH, Parker JI, Dearnaley DP, Eeles R, Huddart R, Khoo V, et al. Patterns of recurrence after prostate bed radiotherapy. *Radiother Oncol*. 2019;141:174-80.

129. Magli A, Moretti E, Tullio A, Giannarini G, Tonetto F, Urpis M, et al. Hypofractionated simultaneous integrated boost (IMRT-SIB) with pelvic nodal irradiation and concurrent androgen deprivation therapy for high-risk prostate cancer: results of a prospective phase II trial. *Prostate Cancer Prostatic Dis*. 2018 [Epub ahead of print].

130. NHS Health Research Authority. PIVOTALBoost Available at: http://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/pivotalboost/ (accessed 2018, 25 May).

131. Vandenbroucke JP. When are observational studies as credible as randomised trials? *Lancet*. 2004;363(9422):1728-31.

132. Desideri I, Salvestrini V, Livi L. Recent advances in de-intensification of radiotherapy in elderly cancer patients. *F1000Res*. 2020;9.

133. Tomic K, Westerberg M, Robinson D, Garmo H, Stattin P. Proportion and characteristics of men with unknown risk category in the National Prostate Cancer Register of Sweden. *Acta Oncol*. 2016;55(12):1461-6.

134. Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL, Jr. Prognostic importance of comorbidity in a hospital-based cancer registry. *Jama*. 2004;291(20):2441-7.

135. Mercieca-Bebber R, King MT, Calvert MJ, Stockler MR, Friedlander M. The importance of patient-reported outcomes in clinical trials and strategies for future optimization. *Patient Relat Outcome Meas*. 2018;9:353-67.

136. Glaser AW, Fraser LK, Corner J, Feltbower R, Morris EJ, Hartwell G, et al. Patient-reported outcomes of cancer survivors in England 1-5 years after diagnosis: a cross-sectional survey. *BMJ Open*. 2013;3(4).

11 APPENDICES

11.1 Supplementary Tables for Research Paper 3

Table 1. Multivariable analysis of determinants of receiving radical treatment for men with high-risk and locally advanced prostate cancer (n=27,248).

	Radical Treatment (%)	Adjusted RR	95% CI	*P**
Diagnosing hospital				0.85
Hub	67.7	1		
Spoke	64.8	0.99	0.91 - 1.08	
Age group (yrs)				**<0.01**
<65	83.9	1		
65-70	81.4	0.97	0.82 - 1.14	
70-75	74.4	0.90	0.85 - 0.95	
>75	41.1	0.52	0.50 - 0.55	
Ethnicity				0.93
White	66.1	1		
Black	62.9	0.94	0.25 - 3.56	
Other	66.3	0.99	0.68 - 1.47	
Socioeconomic deprivation status (national fifths)				0.07
1 (least deprived)	68.8	1		
2	66.8	0.98	0.79 - 1.21	
3	65.5	0.96	0.74 - 1.25	
4	64.2	0.95	0.59 - 1.52	
5 (most deprived)	62.6	0.92	0.67 - 1.28	
Number of co-morbidities (RCS Charlson score)				**<0.01**
0	69.5	1		
1	62.1	0.93	0.90 - 0.97	
≥2	44.4	0.75	0.70 - 0.80	
T stage				**<0.01**
1	44.4	0.78	0.70 - 0.87	
2	65.0	1		
3	70.2	0.99	0.94 - 1.03	
4	38.6	0.70	0.63 - 0.78	
N stage				**<0.01**
0	68.5	1		
1	50.8	0.76	0.70 - 0.82	
Gleason score				**<0.01**
6	56.9	0.76	0.71 - 0.82	
7	72.5	1		
≥8	62.7	0.97	0.73 - 1.27	
PSA (ng/ml)				**0.01**
<10	78.5	1		
10-20	73.8	1.01	0.98 - 1.06	
>20	53.7	0.83	0.70 - 0.98	

*Wald test and likelihood ratio test for binary and categorical variables, respectively

Table 2. Multivariable analysis of determinants of undergoing surgery for men receiving radical treatment for their high-risk or locally advanced prostate cancer (n=17,992).

	Surgery (%)	Adjusted RR	95% CI			*P**
On-site surgery						**<0.01**
No	24.7	1				
Yes	32.0	1.24	1.10	-	1.40	
Age group (yrs)						**<0.01**
<65	52.5	1				
65-70	36.4	0.72	0.67	-	0.77	
70-75	17.8	0.38	0.33	-	0.44	
>75	1.9	0.05	0.03	-	0.07	
Ethnicity						0.07
White	27.9	1				
Black	42.0	1.22	0.30	-	5.05	
Other	32.6	0.98	0.39	-	2.47	
Socioeconomic deprivation status (national fifths)						**0.01**
1 (least deprived)	30.7	1				
2	27.8	0.92	0.84	-	1.00	
3	28.2	0.89	0.81	-	0.97	
4	26.2	0.80	0.70	-	0.91	
5 (most deprived)	28.2	0.80	0.66	-	0.96	
Number of co-morbidities (RCS Charlson score)						**<0.01**
0	29.0	1				
1	29.8	1.09	1.02	-	1.18	
≥2	17.5	0.78	0.67	-	0.92	
T stage						**<0.01**
1	3.1	0.18	0.11	-	0.28	
2	22.7	1				
3	32.5	0.96	0.75	-	1.23	
4	5.9	0.29	0.17	-	0.48	
N stage						**<0.01**
0	29.1	1				
1	22.4	0.84	0.75	-	0.95	
Gleason score						**<0.01**
6	43.7	1.09	0.99	-	1.20	
7	35.3	1				
≥8	18.5	0.67	0.58	-	0.77	
PSA (ng/ml)						**<0.01**
<10	42.6	1				
10-20	29.3	0.84	0.77	-	0.90	
>20	14.0	0.45	0.38	-	0.53	

*Wald test and likelihood ratio test for binary and categorical variables, respectively

Table 3. Multivariable analysis of determinants of receiving high-dose rate brachytherapy boost (HDR-BB) for men with high-risk and locally advanced prostate cancer receiving radiotherapy (n=12,835).

	HDR-BB (%)	Adjusted RR	95% CI			*P**
HDR-BB available						**<0.01**
No	1.2	1				
Yes	7.7	6.16	2.94	-	12.92	
Age group (yrs)						**<0.01**
<65	7.6	1				
65-70	6.2	0.70	0.49	-	1.00	
70-75	4.1	0.44	0.29	-	0.67	
>75	1.4	0.15	0.11	-	0.22	
Ethnicity						0.41
White	4.6	1				
Black	2.8	1.91	0.02	-	205.55	
Other	1.9	0.90	0.03	-	30.85	
Socioeconomic deprivation status (national fifths)						**<0.01**
1 (least deprived)	4.9	1				
2	5.1	0.99	0.67	-	1.47	
3	4.4	0.78	0.41	-	1.50	
4	3.8	0.70	0.51	-	0.96	
5 (most deprived)	2.7	0.55	0.35	-	0.89	
Number of co-morbidities (RCS Charlson score)						**0.07**
0	4.7	1				
1	4.1	1.00	0.69	-	1.45	
≥2	1.9	0.50	0.28	-	0.92	
T stage						**0.02**
1	3.7	0.87	0.58	-	1.29	
2	4.0	1				
3	4.8	1.00	0.62	-	1.62	
4	1.3	0.32	0.13	-	0.80	
N stage						**<0.01**
0	4.7	1				
1	1.8	0.31	0.21	-	0.46	
Gleason score						0.85
6	4.9	0.90	0.61	-	1.34	
7	4.8	1				
≥8	4.0	0.98	0.69	-	1.38	
PSA (ng/ml)						**0.02**
<10	4.4	1				
10-20	4.9	1.18	0.83	-	1.67	
>20	4.1	0.93	0.63	-	1.38	

*Wald test and likelihood ratio test for binary and categorical variables, respectively

11.2 Supplementary Tables for Research Paper 4

Table 1. Multivariable analysis of factors associated with developing gastrointestinal (GI) toxicity following intensity modulated radiation therapy (IMRT).

	Adjusted sHR*	**95% CI**			***P***
Radiotherapy field					0.97
PO-IMRT	1				
PPLN-IMRT	1.00	0.80	-	1.24	
Age group (yr)					0.44
<65	1				
65-70	0.79	0.55	-	1.14	
70-75	0.81	0.59	-	1.11	
>75	0.91	0.65	-	1.28	
Number of comorbidities (RCS Charlson score)					0.11
0	1				
≥1	1.18	0.97	-	1.45	
Deprivation status (national quintiles)					**0.01**
1 (least deprived)	1				
2	1.09	0.86	-	1.38	
3	1.17	0.91	-	1.49	
4	0.83	0.62	-	1.12	
5 (most deprived)	0.68	0.49	-	0.96	
T-stage					0.24
1	1				
2	1.20	0.81	-	1.77	
3	1.01	0.70	-	1.47	
4	1.49	0.82	-	2.68	
N-stage					0.18
0	1				
1	0.82	0.61	-	1.10	
Gleason score					0.27
6	1				
7	1.22	0.78	-	1.93	
8	1.06	0.66	-	1.70	
9	1.35	0.85	-	2.12	
10	1.24	0.56	-	2.72	
Treatment year					0.08
2010	1				
2011	2.04	1.15	-	3.63	
2012	1.72	0.98	-	3.03	
2013	1.62	0.93	-	2.83	
GI procedure 1 yr prior to radiotherapy					**<0.01**
No	1				
Yes	1.77	1.30	-	2.40	

*sHR: subdistribution hazard ratios

Table 2. Multivariable analysis of factors associated with developing genitourinary (GU) toxicity following intensity modulated radiation therapy (IMRT).

	Adjusted sHR*	95% CI			*P*
Radiotherapy field					0.50
Prostate only	1				
Prostate and pelvic lymph nodes	1.10	0.83	-	1.46	
Age group (yr)					0.39
<65	1				
65-70	0.77	0.47	-	1.26	
70-75	0.91	0.60	-	1.39	
>75	1.07	0.67	-	1.70	
Number of comorbidities (RCS Charlson score)					**0.01**
0	1				
≥1	1.39	1.07	-	1.79	
Deprivation status (national quintiles)					0.91
1 (least deprived)	1				
2	0.89	0.65	-	1.24	
3	0.93	0.66	-	1.30	
4	1.05	0.74	-	1.50	
5 (most deprived)	0.96	0.64	-	1.43	
T-stage					0.84
1	1				
2	1.11	0.65	-	1.88	
3	1.17	0.72	-	1.92	
4	0.90	0.37	-	2.18	
N-stage					0.31
0	1				
1	1.19	0.83	-	1.69	
Gleason score					0.88
6	1				
7	1.31	0.70	-	2.45	
8	1.41	0.74	-	2.70	
9	1.36	0.71	-	2.57	
10	1.49	0.54	-	4.15	
Treatment year					0.75
2010	1				
2011	0.73	0.41	-	1.32	
2012	0.78	0.46	-	1.34	
2013	0.82	0.49	-	1.39	
GU procedure 1 yr prior to radiotherapy					**<0.01**
No	1				
Yes	2.04	1.58	-	2.63	

*sHR: subdistribution hazard ratios

11.3 NPCA Patient Survey for Research Papers 6, 7 & 8

https://www.npca.org.uk/content/uploads/2018/12/NPCA-PROMs-SURVEY_FINAL.pdf

NPCA

National Prostate Cancer Audit

Patient Survey

Completing the questionnaire
For each question please tick clearly inside the box that is closest to your views using a black or blue pen. Don't worry if you make a mistake; simply cross out the mistake and put a tick in the correct box.

IMPORTANT INFORMATION TO READ BEFORE COMPLETING THIS QUESTIONNAIRE

By completing this questionnaire, you are giving your consent that the information that you give to us will be used for the purposes explained in the Patient Information Sheet.

You are agreeing that:

- Your response to the questionnaire can be held by the National Prostate Cancer Audit.
- The information that you provide can be combined with the information that is provided by your hospital and other NHS databases, such as the Hospital Episodes Statistics, and the National Cancer Registration and Analysis Service.

The National Prostate Cancer Audit will not release your personal details to other organisations, unless required by law or where there is a clear overriding public interest in disclosure.

Your participation is entirely voluntary. You are free to withdraw the information you have provided to the Audit at any time without giving any reason, without your medical care or legal rights being affected.

To protect your privacy, **please do not write your name or address anywhere on the questionnaire.**

If you have any queries about the questionnaire, please call the FREEPHONE helpline number **on 0800 783 1775**

Patient details

If you are helping to complete this questionnaire on behalf of the patient, please ensure that the information given below is that of the patient and not your own.

Q1. What is your date of birth?

☐☐ / ☐☐ / ☐☐☐☐

D D M M Y Y Y Y

Please ensure this is your **date of birth NOT** today's date

---

Q2. Have you ever been told by a doctor that you have prostate cancer?

Yes	No
☐ 1	☐ 2

If you have ticked no please accept our apologies, we have sent you this questionnaire by mistake. Please do not complete the questionnaire and send it back to us in the envelope provided.

The following questions are about how the prostate cancer was diagnosed and what treatment you have received.

Q3. How was the prostate cancer diagnosed?

I went to the GP with urinary symptoms, such as difficulty starting to urinate, weak flow of urine, urinating frequently	☐ 1
I attended my GP with other symptoms	☐ 2
I had no symptoms and my PSA (blood test) was part of a general health check	☐ 3
I had no symptoms and I asked my GP to measure my PSA	☐ 4
Other	☐ 5

Q4. What treatment(s) have you received for your prostate cancer? Please tick all that apply

Surgery: this involves the removal of the prostate gland by a surgeon	☐ 1
Radiotherapy: this involves the use of X-ray beams or implanting radioactive material in the prostate	☐ 2
Hormone treatment	☐ 3
Active surveillance: close monitoring of the prostate cancer but no current treatment	☐ 4
High intensity focused ultrasound (HIFU): this treatment uses ultrasound waves to heat and destroy cancer tissue in the prostate	☐ 5
Cryotherapy: this treatment uses freezing and thawing to destroy cancer tissue in the prostate	☐ 6
Chemotherapy	☐ 7
Other treatment(s)	☐ 8
I am unsure what treatment I have had	☐ 9

If you had "surgery", go to question 5. If not, skip this question

Q5. What type of surgery did you have?

- Open prostatectomy: this is the removal of the prostate through a cut in the abdominal wall (belly) or a cut in the perineum (area between the testicles and back passage) ☐ 1
- Laparoscopic prostatectomy / Robotic-assisted prostatectomy: this is a keyhole operation to remove the prostate with only a small cut in the abdominal wall (belly) ☐ 2
- I am unsure what type of surgery I had ☐ 3

If you had "radiotherapy", go to question 6. If not, skip this question

Q6. What type of radiotherapy did you have? Please tick all that apply

- External beam radiotherapy: this is radiotherapy that uses equipment that produces high-energy X-rays ☐ 1
- Permanent seed (low-dose) brachytherapy: this involves implanting radioactive material into the prostate permanently ☐ 2
- Temporary (high-dose) brachytherapy: this involves placing a source of high-dose radiation into the prostate for only a few minutes ☐ 3
- I am unsure what type of radiotherapy I have had ☐ 4

If you have been on "active surveillance", go to question 7. If not, skip this question

Q7. What type of active surveillance did you have? Please tick all that apply

- A PSA test every three to six months ☐ 1
- A digital rectal examination within a year ☐ 2
- A prostate biopsy about a year after you were diagnosed ☐ 3
- An MRI scan about a year after you were diagnosed ☐ 4
- I did not have any of these investigations ☐ 5
- I'm unsure what type of active surveillance I have had ☐ 6

Q8. Have you been admitted to hospital as an emergency since you were diagnosed with prostate cancer? Please tick all that apply

- Yes, within the first three months after my prostate cancer was diagnosed ☐ 1
- Yes, more than three months after my prostate cancer was diagnosed ☐ 2
- No ☐ 3

The next set of questions are about symptoms that men with prostate cancer sometimes experience. For each of the questions below please select the response that best applies to you.

The first three questions are about your symptoms immediately before your cancer was diagnosed.

Q9. Overall, how big a problem was your urinary function for you immediately before you were diagnosed with prostate cancer?

- No problem ☐ 1
- Very small problem ☐ 2
- Small problem ☐ 3
- Moderate problem ☐ 4
- Big problem ☐ 5

Q10. Overall, how big a problem were your bowel habits for you immediately before you were diagnosed with prostate cancer?

- No problem ☐ 1
- Very small problem ☐ 2
- Small problem ☐ 3
- Moderate problem ☐ 4
- Big problem ☐ 5

Q11. Overall, how big a problem was your sexual function or lack of sexual function for you immediately before you were diagnosed with prostate cancer?

- No problem ☐ 1
- Very small problem ☐ 2
- Small problem ☐ 3
- Moderate problem ☐ 4
- Big problem ☐ 5

The next set of questions are about your symptoms during the last 4 weeks.

Q12. Over the past 4 weeks, how often have you leaked urine?

- More than once a day ☐ 1
- About once a day ☐ 2
- More than once a week ☐ 3
- About once a week ☐ 4
- Rarely or never ☐ 5

Q13. Which of the following best describes your urinary control during the last 4 weeks?

- No urinary control whatsoever ☐ 1
- Frequent dribbling ☐ 2
- Occasional dribbling ☐ 3
- Total control ☐ 4

Q14. How many pads per day did you usually use to control leakage during the last 4 weeks?

- None ☐ 1
- 1 pad per day ☐ 2
- 2 pads per day ☐ 3
- 3 or more pads per day ☐ 4

Q15. How big a problem, if any, has each of the following been for you during the last 4 weeks?

Please tick one option on each line	No problem	Very small problem	Small problem	Moderate problem	Big problem
Dripping or leaking urine	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pain or burning on urination	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Bleeding with urination	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Weak urine stream or incomplete emptying	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Need to urinate frequently during the day	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Q16. Overall, how big a problem has your urinary function been for you during the last 4 weeks?

- No problem ☐ 1
- Very small problem ☐ 2
- Small problem ☐ 3
- Moderate problem ☐ 4
- Big problem ☐ 5

Q17. How big a problem, if any, has each of the following been for you during the last 4 weeks?

Please tick one option on each line	No problem	Very small problem	Small problem	Moderate problem	Big problem
Urgency to have a bowel movement	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Increased frequency of bowel movements	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Losing control of your stools	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Bloody stools	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Abdominal / Pelvic / Rectal pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Q18. Overall, how big a problem have your bowel habits been for you during the last 4 weeks?

- No problem ☐ 1
- Very small problem ☐ 2
- Small problem ☐ 3
- Moderate problem ☐ 4
- Big problem ☐ 5

Q19. How would you rate each of the following during the last 4 weeks?

Please tick one option on each line	Very poor to none	Very poor	Fair	Good	Very good
Your ability to have an erection?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Your ability to reach orgasm (climax)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Q20. How would you describe the usual quality of your erections during the last 4 weeks?

- None at all ☐ 1
- Not firm enough for any sexual activity ☐ 2
- Firm enough for masturbation and foreplay only ☐ 3
- Firm enough for intercourse ☐ 4

Q21. How would you describe the frequency of your erections during the last 4 weeks?

- I never had an erection when I wanted one ☐ 1
- I had an erection less than half the time I wanted one ☐ 2
- I had an erection about half the time I wanted one ☐ 3
- I had an erection more than half the time I wanted one ☐ 4
- I had an erection whenever I wanted one ☐ 5

Q22. Overall, how would you rate your ability to function sexually during the last 4 weeks?

- Very poor ☐ 1
- Poor ☐ 2
- Fair ☐ 3
- Good ☐ 4
- Very good ☐ 5

Q23. Overall, how big a problem has your sexual function or lack of sexual function been for you during the last 4 weeks?

- No problem ☐ 1
- Very small problem ☐ 2
- Small problem ☐ 3
- Moderate problem ☐ 4
- Big problem ☐ 5

Q24. How big a problem during the last 4 weeks, if any, has each of the following been for you?

Please tick one option on each line	No problem	Very small problem	Small problem	Moderate problem	Big problem
Hot flushes	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Breast tenderness / enlargement	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Feeling depressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Lack of energy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Change in body weight	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Q25. If you were to spend the rest of your life with your symptoms, just the way they are now, how would you feel about that?

- Delighted ☐ 1
- Pleased ☐ 2
- Mostly satisfied ☐ 3
- Mixed, about equally satisfied and dissatisfied ☐ 4
- Mostly dissatisfied ☐ 5
- Unhappy ☐ 6
- Terrible ☐ 7

The following questions are about the care you received since you were diagnosed with prostate cancer.

Q26. When you were diagnosed with prostate cancer, how much information were you given about your condition and possible treatments?

- Not enough ☐ 1
- The right amount ☐ 2
- Too much ☐ 3

Q27. When you were diagnosed with prostate cancer, were you given a choice of different types of treatment?

- Yes ☐ 1
- No, but I would have liked a choice ☐ 2
- I was not given a choice because only one type of treatment was suitable for me ☐ 3
- Not sure / can't remember ☐ 4

Q28. Do you think your views were taken into account when the team of doctors and nurses caring for you were discussing which treatment(s) you should have?

- Yes, definitely ☐ 1
- Yes, to some extent ☐ 2
- No, my views were not taken into account ☐ 3
- I didn't know my treatment was being discussed by a team of doctors / nurses ☐ 4
- Not sure / can't remember ☐ 5

Q29. Were the possible side effects of treatment(s) explained in a way you could understand?

- Yes, definitely ☐ 1
- Yes, to some extent ☐ 2
- No, side effects were not explained ☐ 3
- I did not need an explanation ☐ 4
- Not sure / can't remember ☐ 5

Q30. Were you involved as much as you wanted to be in decisions about your care and treatment?

- Yes, definitely ☐ 1
- Yes, to some extent ☐ 2
- No, but I would have liked to have been more involved ☐ 3
- Not sure / can't remember ☐ 4

Q31. Were you given the name of a Clinical Nurse Specialist who would be in charge of your care?

- Yes - **Go to Q32** ☐ 1
- No - **Go to Q33** ☐ 2
- Don't know / not sure - **Go to Q33** ☐ 3

Q32. When you have important questions to ask your Clinical Nurse Specialist, how often do you get answers you could understand?

- All or most of the time ☐ 1
- Some of the time ☐ 2
- Rarely or never ☐ 3
- I do not ask any questions ☐ 4

Q33. Overall how would you rate your care? Please circle a number

Very poor Very good

0 1 2 3 4 5 6 7 8 9 10

The following questions are about your health overall
Under each heading, please tick the ONE box that best describes your health TODAY

Q34. Mobility

- I have no problems in walking about ☐ 1
- I have slight problems in walking about ☐ 2
- I have moderate problems in walking about ☐ 3
- I have severe problems in walking about ☐ 4
- I am unable to walk about ☐ 5

Q35. Self-Care

- I have no problems with washing or dressing myself ☐ 1
- I have slight problems washing or dressing myself ☐ 2
- I have moderate problems washing or dressing myself ☐ 3
- I have severe problems washing or dressing myself ☐ 4
- I am unable to wash or dress myself ☐ 5

Q36. Usual Activities *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ☐ 1
- I have slight problems doing my usual activities ☐ 2
- I have moderate problems doing my usual activities ☐ 3
- I have severe problems doing my usual activities ☐ 4
- I am unable to do my usual activities ☐ 5

Q37. Pain / Discomfort

- I have no pain or discomfort ☐ 1
- I have slight pain or discomfort ☐ 2
- I have moderate pain or discomfort ☐ 3
- I have severe pain or discomfort ☐ 4
- I have extreme pain or discomfort ☐ 5

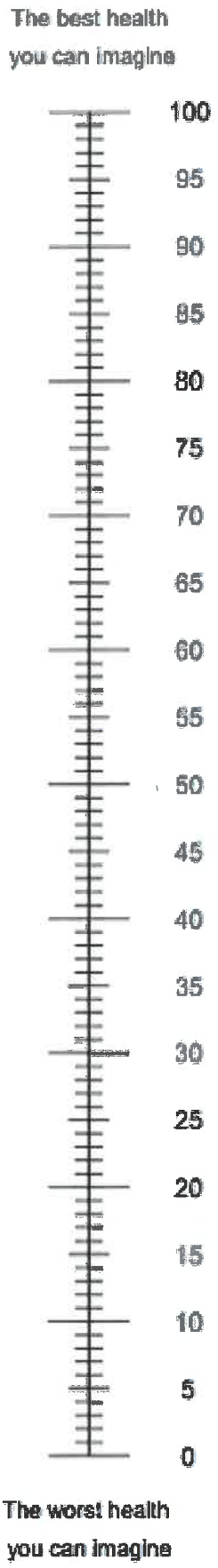
Q38. Anxiety / Depression

- I am not anxious or depressed ☐ 1
- I am slightly anxious or depressed ☐ 2
- I am moderately anxious or depressed ☐ 3
- I am severely anxious or depressed ☐ 4
- I am extremely anxious or depressed ☐ 5

Q39.

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Q40. In general, how would you say your health is?

- Excellent ☐ 1
- Very good ☐ 2
- Good ☐ 3
- Fair ☐ 4
- Poor ☐ 5

Q41. In general, how is your health now, compared to before your prostate cancer diagnosis?

- Much better ☐ 1
- A little better ☐ 2
- About the same ☐ 3
- A little worse ☐ 4
- Much worse ☐ 5

Finally, we would like to ask a few questions about you, so that we may better understand your answers to the questionnaire.

Q42. Have you ever been told by a doctor that you have any of the following? Please tick all that apply

- Heart disease, for example angina, heart attack or heart failure ☐ 1
- High blood pressure ☐ 2
- Problems caused by a stroke ☐ 3
- Leg pain when walking due to poor circulation ☐ 4
- Lung disease, for example asthma, chronic bronchitis or emphysema ☐ 5
- Diabetes ☐ 6
- Kidney disease ☐ 7
- Diseases of the nervous system, for example Parkinson's disease or multiple sclerosis ☐ 8
- Liver disease ☐ 9
- Cancer other than prostate cancer, within the last 5 years ☐ 10
- Depression ☐ 11
- Arthritis ☐ 12

Q43. Which of the following best describes your current home circumstances?

- Married or living with a partner ☐ 1
- In a significant relationship, but not living together ☐ 2
- Living alone / single ☐ 3
- Prefer not to say ☐ 4

Q44. Could we send you a survey in the future to ask about your health and healthcare?

- Yes, and I understand that this does **NOT** mean that I would have to take part in a future survey. ☐ 1
- No, I would prefer you not to contact me again. ☐ 2

Q45. Today's date

☐☐ / ☐☐ / 2 0 ☐☐

D D M M Y Y Y Y

Please ensure this is **today's date NOT** your date of birth

Q46. What is your ethnic group? Choose one option that best describes your ethnic group or background

a. WHITE

- 1 ☐ English
- 2 ☐ Welsh
- 3 ☐ Scottish
- 4 ☐ Northern Irish
- 5 ☐ Irish
- 6 ☐ Gypsy or Irish Traveller
- 7 ☐ Any other White background (please write in box)

b. MIXED

- 8 ☐ White and Black Caribbean
- 9 ☐ White and Black African
- 10 ☐ White and Asian
- 11 ☐ Any other Mixed/Multiple ethnic background (please write in box)

c. ASIAN OR ASIAN BRITISH

- 12 ☐ Indian
- 13 ☐ Pakistani
- 14 ☐ Bangladeshi
- 15 ☐ Chinese
- 16 ☐ Any other Asian background (please write in box)

d. BLACK OR BLACK BRITISH

- 17 ☐ Caribbean
- 18 ☐ African
- 19 ☐ Any other Black background (please write inbox)

e. OTHER ETHNIC GROUP

- 20 ☐ Arab
- 21 ☐ Any other ethnic group (please write in box)

f. 22 ☐ I do not want to answer this question

Thank you very much for completing this questionnaire.
Please return the questionnaire in the FREEPOST envelope provided

11.4 Supplementary Tables for Research Paper 5

Table 1. Patient, tumour and treatment characteristics for survey responders and non-responders.

	Non-responders		Responders		Total	
	n	%	n	%	n	%
No. of patients	1,549	22.1	5,468	87.9	7,017	100
Radiotherapy treatment region						
Prostate only	1,183	76.4	4,196	76.7	5,379	76.7
Prostate & pelvic lymph nodes	366	23.6	1,272	23.3	1,638	23.3
Treatment year						
2014	279	18	997	18.2	1,276	18.2
2015	666	43	2,292	41.9	2,958	42.2
2016	604	39	2,179	39.9	2,783	39.7
Age (years)						
≤60	170	11	295	5.4	465	6.6
61-70	622	40.2	2,076	38	2,698	38.4
71-80	694	44.8	2,840	51.9	3,534	50.4
>80	63	4.1	257	4.7	320	4.6
Comorbidities						
0	1,078	69.6	4,186	76.6	5,264	75
1	335	21.6	920	16.8	1,255	17.9
≥2	136	8.8	362	6.6	498	7.1
Socioeconomic deprivation						
1 (least deprived)	271	17.5	1,279	23.4	1,550	22.1
2	322	20.8	1,404	25.7	1,726	24.6
3	303	19.6	1,216	22.2	1,519	21.6
4	323	20.9	925	16.9	1,248	17.8
5 (most deprived)	330	21.3	644	11.8	974	13.9
Ethnicity						
White	1,301	89.9	4,889	96.3	6,190	94.9
Mixed	3	0.2	13	0.3	16	0.2
Asian	50	3.5	60	1.2	110	1.7
Black	73	5	75	1.5	148	2.3
Other	20	1.4	40	0.8	60	0.9
Missing	102		391		493	
Urinary procedure 1 year prior to radiotherapy						
No	1,189	76.8	4,301	78.7	5,490	78.2
Yes	360	23.2	1,167	21.3	1,527	21.8
Bowel procedure 1 year prior to radiotherapy						
No	1,455	93.9	5,179	94.7	6,634	94.5
Yes	94	6.1	289	5.3	383	5.5

Table 2. Adjusted differences in mean scores for the EPIC-26 urinary incontinence domain for radiotherapy treatment region (PO-IMRT and PPLN-IMRT) and all co-variates.

Variable	Adjusted difference in means	95% CI	*P*
Treatment region			
PO-IMRT	0 (ref)		0.724
PPLN-IMRT	-0.2	-1.2 to 0.8	
Treatment year			
2014	0 (ref)		0.463
2015	0.3	-1.1 to 1.7	
2016	-0.6	-1.9 to 0.7	
Age (years)			
≤60	0 (ref)		**0.013**
61-70	-0.0	-2.4 to 2.4	
71-80	1.0	-0.1 to 2.1	
>80	-3.1	-5.3 to -0.9	
Ethnicity			
White	0 (ref)		0.444
Mixed	1.0	-8.1 to 10.2	
Asian	0.4	-3.7 to 4.4	
Black	-3.7	-8.7 to 1.2	
Other	-3.1	-8.6 to 2.3	
Socioeconomic deprivation (quintiles national distribution)			
1 (least deprived)	0 (ref)		**0.003**
2	-0.4	-1.2 to 2.0	
3	-1.0	-2.4 to 0.4	
4	-1.9	-3.3 to -0.5	
5 (most deprived)	-3.1	-5.0 to -1.3	
Number of comorbidities (RCS Charlson Score)			
0	0 (ref)		**<0.001**
1	-1.6	-3.2 to 0.0	
≥2	-4.5	-6.0 to -3.1	
Urinary procedure 1 year prior to start of radiotherapy			
No	0 (ref)		**<0.001**
Yes	-3.0	-4.3 to -1.7	
Bowel procedure 1 year prior to start of radiotherapy			
No	0 (ref)		0.118
Yes	-2.0	-4.4 to 0.5	
Androgen deprivation therapy			
No	0 (ref)		**0.003**
Yes	2.3	0.8 to 3.8	
Time from survey to treatment (months)			
6-12	0 (ref)		**0.001**
12-18	-2.5	-4.1 to -1.0	
≥18	-2.4	-4.3 to -0.6	

Table 3. Adjusted differences in mean scores for the EPIC-26 urinary irritation/obstruction domain for radiotherapy treatment region (PO-IMRT and PPLN-IMRT) and all co-variates.

Variable	Adjusted difference in means	95% CI	*P*
Treatment region			
PO-IMRT	0 (ref)		0.248
PPLN-IMRT	0.6	-0.4 to 1.6	
Treatment year			
2014	0 (ref)		0.058
2015	1.3	-0.2 to 2.7	
2016	-0.2	-1.6 to 1.2	
Age (years)			
≤60	0 (ref)		**<0.001**
61-70	-3.3	-5.4 to -1.3	
71-80	0.6	-0.4 to 1.7	
>80	-2.1	-4.2 to -0.0	
Ethnicity			
White	0 (ref)		0.069
Mixed	-0.8	-9.5 to 7.9	
Asian	-6.7	-13.1 to -0.4	
Black	-5.5	-10.5 to -0.5	
Other	-2.7	-8.6 to 3.2	
Socioeconomic deprivation (quintiles national distribution)			
1 (least deprived)	0 (ref)		**0.002**
2	0.5	-0.8 to 1.8	
3	-0.7	-2.1 to 0.7	
4	-1.3	-2.9 to 0.2	
5 (most deprived)	-2.7	-4.4 to -1.0	
Number of comorbidities (RCS Charlson Score)			
0	0 (ref)		**<0.001**
1	-0.6	-2.0 to 0.8	
≥2	-3.7	-4.7 to -2.7	
Urinary procedure 1 year prior to start of radiotherapy			
No	0 (ref)		**0.002**
Yes	-1.9	-3.1 to -0.7	
Bowel procedure 1 year prior to start of radiotherapy			
No	0 (ref)		**0.015**
Yes	-2.5	-4.5 to 0.5	
Androgen deprivation therapy			
No	0 (ref)		0.197
Yes	1.0	-0.5 to 2.5	
Time from survey to treatment (months)			
6-12	0 (ref)		0.288
12-18	-0.8	-2.2 to 0.7	
≥18	-1.2	-2.8 to 0.3	

Table 4. Adjusted differences in mean scores for the EPIC-26 sexual function domain for radiotherapy treatment region (PO-IMRT and PPLN-IMRT) and all co-variates.

Variable	Adjusted difference in means	95% CI	*P*
Treatment region			
PO-IMRT	0 (ref)		**0.002**
PPLN-IMRT	-2.3	-3.7 to -0.9	
Treatment year			
2014	0 (ref)		0.352
2015	-0.6	-25. To 1.3	
2016	-1.2	-3.0 to 0.5	
Age (years)			
≤60	0 (ref)		**<0.001**
61-70	5.2	2.5 to 7.8	
71-80	2.9	1.8 to 4.0	
>80	-1.2	-3.0 to 0.5	
Ethnicity			
White	0 (ref)		**0.008**
Mixed	-1.3	-11.2 to 8.6	
Asian	5.2	-0.3 to 10.6	
Black	7.8	2.7 to 12.8	
Other	1.3	-5.2 to -1.5	
Socioeconomic deprivation (quintiles national distribution)			
1 (least deprived)	0 (ref)		**0.010**
2	-1.3	-2.8 to 0.2	
3	-1.9	-3.3 to -0.6	
4	-1.4	-2.9 to -0.1	
5 (most deprived)	-3.4	-5.2 to -1.5	
Number of comorbidities (RCS Charlson Score)			
0	0 (ref)		**<0.001**
1	0.4	-0.9 to 1.7	
≥2	-2.0	-3.2 to -0.8	
Urinary procedure 1 year prior to start of radiotherapy			
No	0 (ref)		0.057
Yes	-1.1	-3.2 to -0.8	
Bowel procedure 1 year prior to start of radiotherapy			
No	0 (ref)		0.385
Yes	-1.0	-3.1 to 1.2	
Androgen deprivation therapy			
No	0 (ref)		0.057
Yes	-1.4	-2.8 to 0.0	
Time from survey to treatment (months)			
6-12	0 (ref)		0.191
12-18	0.4	-1.4 to 2.2	
≥18	1.3	-0.3 to 2.9	

Table 5. Adjusted differences in mean scores for the EPIC-26 bowel function domain for radiotherapy treatment region (PO-IMRT and PPLN-IMRT) and all co-variates.

Variable	Adjusted difference in means	95% CI	*P*
Treatment region			
PO-IMRT	0 (ref)		**0.002**
PPLN-IMRT	0.2	-1.1 to 1.5	
Treatment year			
2014	0 (ref)		0.621
2015	0.6	-0.7 to 1.9	
2016	0.5	-0.8 to 1.9	
Age (years)			
≤60	0 (ref)		0.166
61-70	-3.8	-7.1 to -0.5	
71-80	-0.4	-1.5 to 0.7	
>80	-0.7	-2.8 to 1.4	
Ethnicity			
White	0 (ref)		0.432
Mixed	4.7	-2.1 to 11.6	
Asian	2.6	-2.6 to 7.9	
Black	1.8	-3.6 to 7.2	
Other	-0.4	-6.4 to 5.5	
Socioeconomic deprivation (quintiles national distribution)			
1 (least deprived)	0 (ref)		**0.015**
2	0.3	-0.8 to 1.5	
3	0.7	-0.9 to 2.2	
4	-0.9	-2.7 to 1.0	
5 (most deprived)	-2.3	-4.3 to -0.4	
Number of comorbidities (RCS Charlson Score)			
0	0 (ref)		**<0.001**
1	-1.5	-3.3 to 0.4	
≥2	-5.2	-6.6 to -3.8	
Urinary procedure 1 year prior to start of radiotherapy			
No	0 (ref)		0.056
Yes	-1.5	-3.0 to 0.0	
Bowel procedure 1 year prior to start of radiotherapy			
No	0 (ref)		0.385
Yes	-4.3	-6.6 to -2.0	
Androgen deprivation therapy			
No	0 (ref)		0.060
Yes	-1.1	-2.3 to 0.0	
Time from survey to treatment (months)			
6-12	0 (ref)		0.150
12-18	-1.5	-3.1 to 0.0	
≥18	-1.4	-3.2 to 0.5	

Table 6. Adjusted differences in mean scores for the EPIC-26 hormonal domain for radiotherapy treatment region (PO-IMRT and PPLN-IMRT) and all co-variates.

Variable	Adjusted difference in means	95% CI	*P*
Treatment region			
PO-IMRT	0 (ref)		0.782
PPLN-IMRT	-0.3	-2.1 to 1.6	
Treatment year			
2014	0 (ref)		0.933
2015	-0.3	-2.2 to 1.5	
2016	-0.2	-2.0 to 1.5	
Age (years)			
≤60	0 (ref)		**<0.001**
61-70	-13.0	-16.1 to -10.0	
71-80	-4.4	-6.2 to -2.7	
>80	1.4	-1.7 to 4.4	
Ethnicity			
White	0 (ref)		0.749
Mixed	-3.5	-13.9 to 7.0	
Asian	-3.5	-9.4 to 2.4	
Black	-1.0	-6.6 to 2.4	
Other	0.2	-7.4 to 7.9	
Socioeconomic deprivation (quintiles national distribution)			
1 (least deprived)	0 (ref)		**0.002**
2	-1.1	-2.9 to 0.7	
3	-1.5	-3.3 to -.4	
4	-2.0	-4.0 to -0.1	
5 (most deprived)	-5.3	-8.2 to -2.4	
Number of comorbidities (RCS Charlson Score)			
0	0 (ref)		**<0.001**
1	-1.7	-3.5 to 0.2	
≥2	-8.5	-10.2 to -6.8	
Urinary procedure 1 year prior to start of radiotherapy			
No	0 (ref)		0.150
Yes	-3.0	-4.3 to -1.7	
Bowel procedure 1 year prior to start of radiotherapy			
No	0 (ref)		0.151
Yes	-2.1	-5.0 to 0.8	
Androgen deprivation therapy			
No	0 (ref)		**0.002**
Yes	-3.0	-4.9 to -1.0	
Time from survey to treatment (months)			
6-12	0 (ref)		0.095
12-18	-1.5	-3.2 to 0.3	
≥18	-0.2	-2.7 to 2.2	

Table 7. Adjusted differences in mean EQ-5D-5L scores for radiotherapy treatment region (PO-IMRT and PPLN-IMRT) and all co-variates after IMRT for high-risk and locally advanced prostate cancer.

Variable	Adjusted difference in means	95% CI	*P*
Treatment region			
PO-IMRT	0 (ref)		0.503
PPLN-IMRT	-0.00	-0.01 to 0.01	
Treatment year			
2014	0 (ref)		0.438
2015	0.01	-0.00 to 0.02	
2016	0.01	-0.01 to 0.02	
Age (years)			
≤60	0 (ref)		**<0.001**
61-70	-0.06	-0.08 to -0.03	
71-80	-0.01	-0.02 to 0.00	
>80	0.00	-0.01 to 0.02	
Ethnicity			
White	0 (ref)		0.981
Mixed	-0.01	-0.07 to 0.06	
Asian	-0.01	-0.03 to -0.00	
Black	-0.03	-0.04 to -0.01	
Other	0.01	-0.05 to 0.07	
Socioeconomic deprivation (quintiles national distribution)			
1 (least deprived)	0 (ref)		**<0.001**
2	-0.01	-0.02 to -0.00	
3	-0.01	-0.03 to -0.00	
4	-0.03	-0.04 to 0.01	
5 (most deprived)	-0.06	-0.08 to -0.04	
Number of comorbidities (RCS Charlson Score)			
0	0 (ref)		**<0.001**
1	-0.02	-0.03 to -0.01	
≥2	-0.13	-0.14 to -0.12	
Urinary procedure 1 year prior to start of radiotherapy			
No	0 (ref)		**0.001**
Yes	-0.02	-0.04 to -0.01	
Bowel procedure 1 year prior to start of radiotherapy			
No	0 (ref)		**0001**
Yes	-0.04	-0.06 to -0.02	
Androgen deprivation therapy			
No	0 (ref)		0.959
Yes	0.00	-0.01 to 0.01	
Time from survey to treatment (months)			
6-12	0 (ref)		0.10
12-18	-0.01	-0.02 to 0.01	
≥18	-0.01	-0.03 to 0.00	

11.5 Supplementary Tables for Research Paper 6

Table 1. OPCS-4 procedure codes and ICD-10 diagnosis codes used to identify gastrointestinal toxicity.

OPCS-4 Procedure Code	**Code Definition**
At least grade 2	
H201-4,6-9,H212,H221-9	Endoscopy of colon
H231-9,H242,8-9,H251,8-9	Sigmoidoscopy of lower bowel
H261-9,H279,H281,9	Sigmoidoscopy of sigmoid colon
M372	Repair of vesicocolic fistula
M375	Repair of fistula of bladder NEC
At least grade 3	
H202,232,262,264	Cauterisation/cauterisation/cryotherapy of lesion of colon/lower bowel/sigmoid colon
H212	Coagulation of blood vessel of colon/lower bowel
M372	Repair of vesicocolic fistula
M375	Repair of fistula of bladder NEC
Y088-9	Other specified/unspecified laser therapy to organ NOC
Y111-2	Cauterisation/cryotherapy of organ NOC
Y131-2,6	Cauterisation/cryotherapy/photodynamic therapy of lesion of organ NOC
ICD-10 Diagnosis Code	
K520	Gastroenteritis and colitis due to radiation
K528-9	Other specified/unspecified noninfective gastroenteritis and colitis
K603-4	Anal/rectal fistula
K624-6	Stenosis/haemorrhage/ulcer of anus and rectum
K627	Radiation proctitis
K628-9	Other specified/unspecified disease of rectum and anus
K632	Intestinal fistula
N321	Vesicointestinal fistula

Table 2. OPCS-4 procedure codes and ICD-10 diagnosis codes used to identify genitourinary toxicity.

OPCS-4 Procedure Code	**Code Definition**
At least grade 2	
M455	Diagnostic endoscopic examination of bladder using rigid cystoscope
M458-9	Other specified/unspecified diagnostic endoscopic examination of bladder
M478-9	Other specified/unspecified urethral catheterisation of bladder
M512	Endoscopic suspension of neck of bladder
At least grade 3	
M444-9	Endoscopic removal of blood clot from bladder
M448-9	Other specified/unspecified other therapeutic endoscopic operations on bladder
M471	Urethral irrigation of bladder
M481	Suprapubic aspiration of bladder
M642	Implantation of artificial urinary sphincter into outlet of male bladder
M643	Insertion of prosthetic collar around outlet of male bladder
M646	Reconstruction of neck of male bladder NEC
M648-9	Other specified/unspecified other open operations on outlet of male bladder
M651-5,8-9	Endoscopic resection of prostate/outlet of male bladder
M662	Endoscopic incision of outlet of male bladder NEC
M668-9	Other specified/unspecified other therapeutic endoscopic operations on outlet of male bladder
M679	Unspecified other therapeutic endoscopic operations on prostate
M763	Optical urethrotomy
M764	Endoscopic dilation of urethra
M768-9	Other specified/unspecified therapeutic endoscopic operations on urethra
M792	Dilation of urethra NEC
M793	Calibration of urethra
M794	Internal urethrotomy NEC
ICD-10 Diagnosis Code	
N02	Recurrent and persistent haematuria
N304	Irradiation cystitis
N328	Other specified disorders of bladder
N320	Bladder neck obstruction
N35	Urethral stricture
N393-4	Stress/other specified urinary incontinence
N398	Other specified disorders of urinary system
N421	Congestion and haemorrhage of prostate
N991	Post-procedure urethral stricture
R31	Unspecified haematuria
R32	Unspecified urinary incontinence
R33	Urinary retention

Table 3. At least grade 3 gastrointestinal and genitourinary toxicity in patients who received EBRT only, HDR-BB, or LDR-BB.

Outcome measure	5-Year Cumulative Incidence (%)	95% CI	sHR (95% CI)	*P*
Gastrointestinal toxicity				
EBRT	3.2	3.1 to 3.4	1	**0.004**
HDR-BB	1.8	1.4 to 2.4	0.58 (0.39 to 0.88)	
LDR-BB	5.1	2.9 to 8.2	1.49 (0.94 to 2.37)	
Genitourinary toxicity				
EBRT	4.6	4.4 to 4.8	1	**<0.001**
HDR-BB	9.0	7.9 to 10.2	2.35 (1.64 to 3.36)	
LDR-BB	11.1	7.8 to 15.1	3.15 (1.68 to 5.91)	

11.6 Supplementary Table for Research Paper 7

Table 1. Patient, tumour and treatment characteristics for survey responders and non-responders.

	Non-responders		Responders		Total	
	n	%	n	%	N	%
No. of patients	3,851	22.5	13,259	77.5	17,110	100
Treatment year						
2014	761	19.8	2,633	19.9	3,394	19.8
2015	1,348	35	4,513	34	5,861	34.3
2016	1,742	45.2	6,113	46.1	7,855	45.9
Age (years)						
≤60	359	9.3	560	4.2	919	5.4
61-70	1,423	37	4,478	33.8	5,901	34.5
71-80	1,864	48.4	7,432	56.1	9,296	54.3
>80	205	5.3	789	6	994	5.8
Comorbidities						
0	2,659	69	10,021	75.6	12,680	74.1
1	832	21.6	2,332	17.6	3,164	18.5
≥2	360	9.3	906	6.8	1,266	7.4
Socioeconomic deprivation						
1 (least deprived)	660	17.1	3,223	24.3	3,883	22.7
2	798	20.7	3,262	24.6	4,060	23.7
3	784	20.4	2,885	21.8	3,669	21.4
4	804	20.9	2,226	16.8	3,030	17.7
5 (most deprived)	805	20.9	1,663	12.5	2,468	14.4
Ethnicity						
White	3,200	88.4	11,932	96	15,132	94.3
Mixed	19	0.5	30	0.2	49	0.3
Asian	148	4.1	156	1.3	304	1.9
Black	194	5.4	225	1.8	419	2.6
Other	59	1.6	80	0.6	139	0.9
Missing	102		391		493	
Urinary procedure 1 year prior to radiotherapy						
No	3,014	78.3	10,498	79.2	13,512	79
Yes	837	21.7	2,761	20.8	3,598	21
Bowel procedure 1 year prior to radiotherapy						
No	3,636	94.4	12,571	94.8	16,207	94.7
Yes	215	5.6	688	5.2	903	5.3
Cancer risk profile						
Intermediate-risk	2,576	66.9	8,941	67.4	11,517	67.3
High-risk/locally advanced	1,275	33.1	4,318	32.6	5,593	32.7
Treatment						
EBRT only	3,671	95.3	12,503	94.3	16,174	94.5
HDR brachytherapy boost	180	4.7	756	5.7	936	5.5
Radiotherapy type						
3D conformal	218	5.7	713	5.4	931	5.4
IMRT	3,633	94.3	12,546	94.6	16,179	94.6