**TITLE**

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.

**RUNNING TITLE**

High-dose rate brachytherapy boost for prostate cancer.

**KEYWORDS**

Prostate cancer; brachytherapy boost; high-dose-rate; external beam radiation therapy; patient-reported outcomes.

**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 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.

**INTRODUCTION**

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 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 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 (**Figure 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 **Figure 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 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 and 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), 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, 33). 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 (**Figure 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 ≤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 (**Figure 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 Figure 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 Figure 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 ≥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.

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 (34). 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 treatment) GU toxicity, the majority of this acute toxicity is only transient (12, 35). 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 (35, 36).

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 (35, 37, 38). 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 (39).

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, and so differences in baseline function within a strict cohort of men receiving EBRT are likely to be even smaller (40).

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.

**FUNDING:**

This work was supported by the National Institute for Health Research (grant number DRF-2018-11-ST2-036) and the Medical Research Council (grant number MR/S020470/1). BB was partly supported by an Academic Clinical Fellowship from the National Institute for Health Research. HP was supported by the University College London Hospitals/University College London Comprehensive Biomedical Research Centre. JvdM was partly supported by the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care North Thames. The views expressed in this article are solely those of the authors.

**ACKNOWLEDGEMENTS:**

We thank NHS staff for their support in collecting the clinical data, the National Cancer Registration and Analysis Service ([www.ncras.nhs.uk](http://www.ncras.nhs.uk)) for providing cancer registry and radiotherapy data and NHS Digital ([www.digital.nhs.uk](http://www.digital.nhs.uk)) for providing Hospital Episode Statistics. MGP, JN, TC, AS, BB, PC, NWC, HP, AA and JvdM are members of the Project Team of the National Prostate Cancer Audit ([www.npca.org.uk](http://www.npca.org.uk)). The National Prostate Cancer Audit is commissioned by the Healthcare Quality Improvement Partnership ([www.hqip.org.uk](http://www.hqip.org.uk)) as part of the National Clinical Audit and Patient Outcomes Programme, and funded by NHS England and the Welsh Government. Neither HQIP nor NHS England or the Welsh Government had any involvement in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication. The researchers had full independence from the Healthcare Quality Improvement Partnership.

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](http://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](http://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 datasets.

**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 2017. [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. Rothmann MD, Wiens BL, Chan ISC. Design and Analysis of Non-Inferiority Trials: Chapman and Hall/CRC; 2011.

34. 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>.

35. 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.

36. 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.

37. 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.

38. 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.

39. 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.

40. 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.

**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 to 11 | 1,378 | 11.0 | 125 | 16.5 | 1,503 | 11.3 |
| 12 to 18 | 7,006 | 56.0 | 389 | 51.5 | 7,395 | 55.8 |
| ≥18 | 4,119 | 32.9 | 242 | 32.0 | 4,361 | 32.9 |

**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 with HDR-BB versus EBRT only** | |
|  | **EBRT only** | **EBRT with HDR-BB** | **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.

**Figure 1.** Patient chart of cohort selection

**Figure 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.