**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.

**RUNNING TITLE**

Brachytherapy boost for prostate cancer.

**KEYWORDS**

Prostate cancer; high-dose rate brachytherapy boost; low-dose rate brachytherapy boost; external beam radiation therapy

**ABSTRACT**

*Purpose:* External beam radiotherapy (EBRT) with brachytherapy boost reduces cancer recurrence in patients diagnosed with prostate cancer compared to EBRT monotherapy. However, randomised 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, radiotherapy data, administrative hospital data and mortality records of 54,642 patients diagnosed 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 (SREs), and prostate cancer-specific mortality (PCSM) at five years with adjustment for patient and tumour characteristics. Linear regression was used to compare EPIC-26 domain scores (scale from 0 to 100, higher scores indicating better function).

*Results:* 5-year GI toxicity was significantly increased after LDR-BB (32.3%) compared to HDR-BB (16.7%) or EBRT monotherapy (18.7%). 5-year GU toxicity was significantly increased after both LDR-BB (15.8%) and HDR-BB (16.6%), compared to 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, and EBRT monotherapy: 84.4) and the mean patient-reported urinary obstruction/irritation function scores (LDR-BB: 72.2, HDR-BB: 78.9, and EBRT monotherapy: 83.8). 5-year incidences of SREs and PCSM were significantly lower after HDR-BB (2.4% and 2.7%, respectively) compared to EBRT monotherapy (2.8% and 3.5%, respectively).

*Conclusions:* LDR-BB has worse GI and GU toxicity and HDR-BB has worse GU toxicity compared to EBRT monotherapy. HDR-BB has a lower incidence of SREs and PCSM than EBRT monotherapy.

**INTRODUCTION:**

Advances in radiotherapy 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 in addition to external beam radiation therapy (EBRT). Three randomised controlled trials (RCTs) have compared EBRT only (hereafter referred to as EBRT monotherapy irrespective of concomitant hormone therapy) to EBRT with a brachytherapy boost, and all showed a benefit in terms of biochemical cancer control (2-8).

Observational data suggests lower prostate cancer-specific mortality (PCSM) following EBRT with either a high-dose rate (HDR-BB) or low-dose rate brachytherapy boost (LDR-BB) compared to EBRT monotherapy (9-15). However, no RCT or large-scale observational studies have compared brachytherapy boost types directly. The only current evidence is a retrospective single centre study comparing HDR-BB to LDR-BB delivered across two different time periods (16). LDR-BB had superior biochemical progression-free survival than 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 to EBRT monotherapy (7, 8), whilst HDR-BB has been shown to have a better GI toxicity profile compared to EBRT monotherapy (3, 17-19).

HDR-BB and LDR-BB have not been compared directly with respect to toxicity, functional and cancer outcomes. We therefore used electronic healthcare 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 (SREs) and PCSM following HDR-BB, LDR-BB, or EBRT monotherapy (20).

**MATERIALS AND METHODS:**

*Patient population*

This study used English Cancer Registry data (21), the National Radiotherapy Dataset (RTDS) (22) and Hospital Episode Statistics (HES) (23) linked at patient level to follow up men with prostate cancer who were treated with radical radiotherapy 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.

59,381 men who received radical radiotherapy for non-metastatic 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 (PSA) data prior to 2014 and the inability to further subdivide T stage beyond T1-4 (i.e. T2a, T2b or T2c (26). This stratification system assigns ‘intermediate-risk’ to men with T2, Gleason score 7 and ‘locally advanced’ to men with T3, T4 or N1. Men with a Gleason score ≥8 (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 radiotherapy (n=168) or brachytherapy centre (n=35), those with a concomitant diagnosis of bladder cancer (n=1,686) or those where the radiotherapy regimen was unknown (n=2,848). Men who received a brachytherapy boost 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 (Figure 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) (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 non-responders at 4 and 8 weeks. The survey was sent out to 15,041 eligible men who had received treatment at least 6 months prior to the survey of whom 11,676 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 following radiotherapy (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 following radiotherapy (Supplementary Material). 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 non-invasive interventions) (30).

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

*Functional outcomes*

We used three EPIC-26 domains (urinary incontinence, urinary obstruction/irritation and bowel function), each summarised 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 radiotherapy based on ICD-10 diagnostic and OPCS-4 procedure codes in HES and radiotherapy 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 where 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 radiotherapy and brachytherapy doses. Patients were allocated to EBRT monotherapy or brachytherapy boost groups based on recognised EBRT regimens and brachytherapy doses (Figure 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 organisational survey and following within centre 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 brachytherapy boost and LDR brachytherapy boost, respectively.

Data items in the HES records in the year before diagnosis were used to determine the number of comorbidities according to the RCS Charlson score (33). Socioeconomic deprivation status was determined for patients from the English 2015 Index of Multiple Deprivation (IMD) (34). T-stage, N-stage, M-stage and Gleason grade were identified from the cancer registry data. Previous GI and GU treatments 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 cumulative incidence of GI and GU toxicity, SREs and PCSM from the start of radiotherapy until the end of follow-up for a maximum of five years. We considered death from any cause as a competing event when analysing toxicity and SREs, and death from other causes when analysing PCSM. Fine and Gray competing risk regression analysis was used to estimate subdistribution hazard ratios (sHR) with 95% confidence intervals (CIs) 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 tumour characteristics outlined in Table 1. Age was included as a linear and a quadratic term. Time between the start of radiotherapy treatment and the patient survey (6-12, 12-18 and >18 months) 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 three treatment groups (37).

Missing data were imputed using multiple imputation by chained equations (38). 10 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 prior to linear regression so that all survey responders were included.

**RESULTS:**

*Patient population*

Of the 54,642 men who received EBRT between 2010 and 2016, 2,765 (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 (inter-quartile range: 66 to 75), 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 above.

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 2,765 men in the HDR-BB group, 1,225 (44.3%) received 46 Gy in 23 fractions as their EBRT dose and 1,197 (43.3%) received a hypofractionated regimen of 37.5 Gy in 15 fractions. 1,206 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 men (8.8%) received 50.4 Gy in 28 fractions and 23 men (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 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*<0.05). 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 above), whereas the LDR-BB group had the least advanced cancers (32.5% T3/4 and 21.1% Gleason grade of 8 or above).

*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*<0.001). 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*<0.001). 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 following HDR-BB compared to EBRT monotherapy (Supplementary Material).

*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*=0.304; Table 3).

There were statistically significant differences in the mean EPIC-26 urinary irritation/obstruction scores (*P*<0.001). Men who received EBRT monotherapy had the highest mean scores (83.8) (i.e. 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) (i.e. 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 and cancer outcomes following 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 radiotherapy 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 LDR-BB was associated with worse GI toxicity at five years compared to either HDR-BB or EBRT monotherapy. The validity of this finding was supported by the results from the National Prostate Cancer Audit patient survey where 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 to LDR brachytherapy, and is also not subject to seed migration (39).

Further to this, men who received a brachytherapy boost, irrespective of type, were more likely to experience GU toxicity at five years compared to men who received EBRT monotherapy. HDR-BB was associated with a lower cumulative incidence of both SREs and PCSM at five years compared to EBRT monotherapy or LDR-BB.

*Comparison with other studies*

Our finding that LDR-BB has poorer GI and GU outcomes compared to EBRT monotherapy is consistent with results from the ASCENDE-RT study (2017), which used permanent Iodine-125 seeds. However, the trend towards worse GI toxicity in ASCENDE-RT was nonsignificant (7). An older RCT of LDR-BB, which used temporary Iridium-192 wires, also found worse GI toxicity following 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, following HDR-BB compared to EBRT monotherapy. Regarding GU toxicity, results were comparable between groups (3-5). Although our results show that urinary irritation/obstruction domain scores were worse following 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 to toxicity. The trial supports our findings, with LDR-BB having worse GI toxicity (at least grade 3) compared to HDR-BB (cumulative incidence 8% and 4%, respectively). However, differences did not reach statistical significance (16).

Two of the three RCTs discussed were conducted before 2012 when lower radiation doses (55 and 66 Gy) and older 4-field or 3D-conformal techniques were used. Both these trials showed better biochemical progression-free survival following a brachytherapy boost compared to EBRT monotherapy where 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 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 centre observational study of 287 men, directly comparing men receiving HDR-BB (2007 to 2012) and LDR-BB (1996 to 2007), concluded that LDR-BB may provide more effective prostate-specific antigen control at five 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 to either HDR-BB or EBRT monotherapy.

In support of other observational studies, we found a difference in cancer outcomes at five years between EBRT monotherapy and HDR-BB (9-15). Five years is a relatively short time-frame 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 generalisability of its results. In addition, more than 90% of the patients who receive radiotherapy in England are treated within the National Health Service and these episodes are collected within the RTDS. All of the men receiving a recognised radiotherapy regimen during the study period were therefore 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 to 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 maximises their specificity and minimises the risk of misclassification bias. Furthermore, toxicity results of at least grade 3 aligns well with the overall toxicity results (at least grade 2) across treatment groups. Finally, the agreement between the patient-reported outcome measures and the toxicity measures derived from national electronic healthcare 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 tumour 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, it was also not possible using these datasets 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 IMRT and have information on the inclusion of pelvic lymph nodes with the treatment field, which could impact on 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 brachytherapy boost 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 brachytherapy boost and the true impact of brachytherapy boost on GI and GU toxicity may be even bigger 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 to clinical notes (41). The methods used in this paper 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 centre has shown that this coding framework can reliably identify brachytherapy episodes. Finally, some of the adjustment variables also had missing values but we feel that multiple imputation was able to limit the impact of any potential confounding.

**CONCLUSION:**

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

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**Figure 1.** Flowchart of patients included in the study.

**Figure 2.** Cumulative incidence of at least grade 2 gastrointestinal and genitourinary toxicity after EBRT monotherapy, HDR-BB, or LDR-BB.

**Figure 3.** Cumulative incidence of skeletal-related events and prostate cancer-specific mortality after EBRT monotherapy, HDR-BB, or LDR-BB.