NHS England

Evidence review: Low dose brachytherapy boost for intermediate and high risk localised prostate cancer

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Contents

1 Introduction

Introduction

- Prostate cancer is one of the most common cancers in men. Prognosis and treatment options vary depending on grade of tumour and stage of diagnosed cancer.
- Localised prostate cancer is completely contained within the prostate gland. It can be risk stratified based on Prostate Specific Antigen (PSA) level[1], Gleason score[2] and T stage[3].
- Table 1 summarises the risk stratification criteria for intermediate- and high-risk prostate cancer. Slightly different T stage criteria for intermediate and high risk are used by NICE (NICE, 2014b) and by the USA National Comprehensive Cancer Network (NCCN, 2016).

Table 1. Risk stratification of localised prostate cancer according to NICE (NICE, 2014b) and NCCN (NCCN, 2016)

Risk group is indicated by the presence of at least one of the specified criteria.

	NICE		NCCN	
	Intermediate risk	**High risk**	**Intermediate risk**	**High risk**
PSA	10-20	>20	10-20	>20
Gleason score	7	>7	7	>7
T stage	T2b	≥T2c	T2b/c	≥T3

Existing guidance from the National Institute of Health and Care Excellence (NICE)

- The 2014 NICE Clinical Guideline (CG175) 'Prostate Cancer: diagnosis and management' includes the following recommendations regarding brachytherapy:
  - 'Consider high dose rate brachytherapy in combination with external beam radiotherapy (EBRT) for men with intermediate- and high-risk localised prostate cancer.'
  - 'Do not offer brachytherapy alone to men with high-risk localised prostate cancer.'

  It does not make any recommendation about low dose rate brachytherapy (NICE 2014b). This CG is currently under review (expected publication date April 2019).
- NICE Interventional Procedures Guidance (IPG132) on low dose rate brachytherapy for localised prostate cancer, published in 2005, stated that 'current evidence on the safety and short- to medium-term efficacy of low dose rate brachytherapy for localised prostate

[1] PSA is a protein which is expressed by both normal and malignant prostate cells. An increased serum PSA may be an indicator of prostate cancer but PSA levels may rise for other reasons such as infection or glandular enlargement due to benign prostatic hyperplasia, and levels can also fluctuate over time. A raised PSA is therefore not a specific marker for prostate cancer. A more rapid rise in PSA level may indicate more aggressive disease or post-therapy relapse (NICE 2014a).

[2] The Gleason score reflects the histological appearance of prostate biopsies. The currently used system uses scores from ≤6 to 10 with higher scores indicating higher risk disease.

[3] The T stage indicates the extent and spread of the tumour. The main grades are T0-T4, each with subcategories. T0 indicates that there is no evidence of a primary tumour, T1 is a tumour which is not clinically apparent either by palpation or imaging, T2 is a tumour confined within the prostate, T3 is a tumour which extends through the prostatic capsule, and a T4 tumour is fixed or invades adjacent structures other than the seminal vesicles. Staging also indicates the extent of involvement of local lymph nodes (N stage) and presence or absence of distant metastases (M stage) (NICE 2014a).

cancer appears adequate to support its use, provided that the normal arrangements are in place for consent, audit and clinical governance' (NICE 2005). It adds that 'current management options for localised prostate cancer include radiotherapy, radical prostatectomy and 'watchful waiting'. Radiation therapy can take the form of external-beam radiotherapy or brachytherapy. Brachytherapy may be given at either low or high dose rates. Low dose rate brachytherapy may be used alone (monotherapy) or in combination with external-beam radiotherapy.'

Indication and epidemiology

- Prostate cancer is the most common cancer in men in the UK, with 47,151 new cases in 2015 (Cancer Research UK, 2019).
- Age-specific incidence rates rise steeply from around age 50-54, peak in the 75-79 age group, and subsequently drop in the 80-84 age group, before increasing steadily again. The highest rates are in the 90+ age group. Age-standardised incidence rates in the UK increased by 6% between 2003-05 and 2013-15 (Cancer Research UK, 2019).
- Prognosis with prostate cancer is variable and depends on the grade of the tumour and stage of the diagnosed cancer. Symptoms, if they occur, include those related to urinary outflow obstruction and, in the case of metatastic disease, bone pain.
- About 66% of localised prostate cancer in the UK is estimated to be intermediate- or high-risk (Carter, 2011). This equates to around 27,500 patients per year in the UK (NHS England, 2018).

Standard treatment and pathway of care

- Treatment options for prostate cancer depend on the stage of the cancer. For localised prostate cancer, treatment options include active surveillance, radiotherapy, and radical prostatectomy, and vary according to the patient's level of risk.
- Men with intermediate-risk localised prostate cancer may be offered radical prostatectomy or radical radiotherapy. Alternatively, if they do not wish to have either of these procedures immediately, they may be offered active surveillance (NICE, 2014b).
- Radical prostatectomy or radical radiotherapy are also options for men with high-risk localised prostate cancer when there is a realistic prospect of long-term disease control.
- NICE recommend that EBRT with curative intent should use a minimum dose of 74 Gy to the prostate at no more than 2 Gy per fraction (NICE, 2014b) (conventionally fractionated radiotherapy).
- Following a review of more recently published randomised controlled trials (RCTs), NHS England now recommend a hypofractionated EBRT regime delivering 60Gy at 3Gy per fraction in 20 daily fractions (NHS England, 2017).
- Men who are treated for intermediate- or high-risk localised prostate cancer with radical radiotherapy should also be offered androgen deprivation therapy. The two treatments are offered together, rather than either radical radiotherapy or androgen deprivation therapy alone.
- Around 30% of patients with prostate cancer currently receive radiotherapy as part of their primary treatment (Cancer Research UK, 2019).

The intervention (and licensed indication)

- Low dose rate brachytherapy (LDRBT) is a form of radiotherapy in which delivery of radiation is targeted directly to the prostate gland through the implantation of small radioactive pellets (NICE 2005). It may be given as primary radiotherapy or in combination with external beam radiotherapy.
- LDRBT involves transrectal ultrasound (TRUS) guided insertion of permanent Iodine 125 or Palladium 103 seeds via the perineum into the prostate, carried out under spinal or general anaesthetic. The seeds release radiation into the prostate over the following months with a dose around 90-110 Gy.

Rationale for use

- The aim of LDRBT is to provide a localised radiotherapy boost which can be targeted directly at the areas requiring treatment, with the aim of providing an increased dose of radiotherapy to the cancer with reduced risk of damage to surrounding normal tissues like the rectum or bladder.

2 Summary of results

- Six papers were included in this rapid evidence review. Three papers reported findings from the ASCENDE-RT trial which compared external beam radiotherapy and low dose rate prostate brachytherapy boost (LDRPB) with dose-escalated external beam radiotherapy (DE-EBRT) in 398 patients with intermediate and high risk localised prostate cancer (Morris et al 2017; Rodda et al 2017a; Rodda et al 2017b).
- In addition two retrospective studies have been included. These reported longer-term follow-up of outcomes similar to those in ASCENDE-RT for high or intermediate risk prostate cancer patients treated with LDRPB or DE-EBRT (Luo et al 2018; Abugharib et al 2017). A large database analysis of over 25,000 subjects treated with either LDRPB or DE-EBRT and outcomes reported to seven years has also been included (Johnson et al 2017).

Clinical effectiveness

- **Overall survival** (three studies, n=398, n=25,038, n=320). In the ASCENDE-RT RCT there was no significant difference in overall survival (OS) in patients randomised to LDRPB compared with DE-EBRT at 5 years (91.3% vs 88.7%), 7 years (85.7% vs 81.5%) and 9yrs (77.9% vs 73.6%) (p=0.293) (Morris et al, 2017). There was a significant benefit in OS at 7 years for patients receiving LDRPB compared with DE-EBRT in the large database study (82% vs 73%, Hazard ratio (HR) 0.70 (95% CI 0.64-0.77)) (Johnson et al 2017). There was a significant OS benefit from 7 years onwards, up to 15 years follow-up, in the retrospective study by Luo et al (2018), with median OS of 12.3 years for LDRPB and 9.1 years for DE-EBRT (HR 6.358, (95% CI 5.733- 6.627), p<0.001).
- **Biochemical progression**[4] (three studies, n=398, n=579, n=320). Two studies reported significantly better biochemical progression-free survival (bPFS) for the LDRPB group,

[4] Being free of biochemical progression was defined as a PSA level which rose <2 ng/mL above the nadir level for that patient. Morris et al (2017) also included in their definition the absence of any imaging or clinical recurrence and no receipt

compared with DE-EBRT. In the ASCENDE-RT trial bPFS at 5, 7 and 9 years post-treatment was 88.7% +/- SD 4.8, 86.2% +/- SD 5.4 and 83.3% +/- SD 6.6 for patients randomised to LDRPB compared with 83.8% +/- SD 5.6, 75.0% +/- SD 7.2 and 62.4% +/- SD 9.8 for DE-EBRT (log-rank p<0.001; HR 2.04 (95%CI 1.25-3.33, p=0.004)) (Morris et al 2017). In a study of intermediate-risk patients, Abugharib et al (2017) reported bPFS at 5 and 10 years of 94.1% (95%CI 90.4-97.8) and 91.7% (95%CI 86.8-96.6) for patients receiving LDRPB, compared with 89.2% (95%CI 85.9-92.5) and 75.4% (95%CI 70.1-80.7) for those receiving DE-EBRT (p=0.014).

On follow-up up to 15 years, median time to biochemical progression was 9.8 years (95%CI 8.5-10.7) for patients receiving LDRPB compared with 6.5 years (95%CI 4.8-8.1) for DE-EBRT, a significant difference (HR: 5.126 (95%CI 4.251-6.306), p < 0.001) (Luo et al 2018).

- **Biochemical failure** (one study, n=398). Morris et al (2017) reported a significantly higher risk of biochemical failure in subjects who were randomised to DE-EBRT compared with those randomised to LDRPB. On multivariable analysis the HR of biochemical failure in those randomised to DE-EBRT vs those randomised to LDRPB was 2.04 (95%CI 1.25-3.33, p=0.004).
- **Metastasis-free survival**[5] (two studies, n=398, n=579). No significant differences were found in metastasis-free survival (MFS). MFS at 9 years was 88.6% +/- SD 5.6 for patients randomised to LDRPB vs 84.8% +/- SD 7.6 for patients randomised to DE-EBRT in the ASCENDE-RT trial (Morris et al 2017). Abugharib et al (2017) found distant MFS in patients treated with LDRPB vs DE-EBRT of 95.2% (95%CI 91.7-98.7) vs 98.3% (95%CI 96.9-99.7) at 5 years and 95.2% (95%CI 91.7-98.7) vs 95.3% (95%CI 92.8-97.8) at 10 years (p=0.21).
- **Prostate cancer-specific survival** (one study, n=398). There was no significant difference in prostate cancer-specific survival (PCSS), which at 9 years follow-up was 94.8% +/-SD 4.0 in the LDRPB group, and 92.1% +/-SD 5.6 in the DE-EBRT group (Morris et al 2017).
- **Local progression-free survival** (one study, n=579). Local progression-free survival (LPFS) in intermediate risk patients receiving LDRPB vs DE-EBRT was 100.0% (95%CI 100.0-100.0) vs 99.4% (95%CI 98.6-100.0) at 5 years, and 100.0% (95%CI 100.0-100.0) vs 94.9% (95%CI 92.2-97.6) at 10years (p=0.042) (Abugharib et al 2017).

Safety

- **Acute genitourinary (GU) morbidity** (two studies, n=383, n=320). Up to 6 months after treatment, 19.1% of LDRPB patients compared with 40.5% of DE-EBRT patients in ASCENDE-RT were symptom-free (p<0.0001), and 30.0% of LDRPB patients compared with 15.8% of DE-EBRT patients had moderate GU symptoms (p<0.0001) (Rodda et al 2017a). Luo et al (2018) also found significantly less acute GU morbidity among DE-EBRT patients.
- **Late genitourinary (GU) morbidity** (three studies, n=383, n=320, n=579). Up to 5 years after starting treatment 20.6% LDRPB patients compared with 29.6% DE-EBRT patients in ASCENDE-RT had no late GU symptoms (p=0.003), 32.8% LDRPB patients compared with 20.6% DE-EBRT patients had moderate GU symptoms (p=0.002) and 18.4% LDRPB patients compared with 5.2% DE-EBRT patients had moderately severe (p<0.001) GU

of any form of secondary treatment for prostate cancer after completion of protocol interventions. Luo et al (2018) also included, for cases with no previous PSA level decrease, a less than 1.25-fold elevation compared to baseline values.

[5] Morris et al (2017) did not define this outcome or describe how metastases were identified. Abugharib et al (2017) stated that distant metastases were confirmed by imaging and/or biopsy.

symptoms (Rodda et al 2017a). The prevalence of late grade ≥3 (moderately severe or worse) GU adverse events at 2 years was LDRPB 7.0% vs DE-EBRT 1.1% (p=0.005), and at 5 years was LDRPB 8.6% vs DE-EBRT 2.2% (p=0.058). Luo et al (2018) found only one symptom (frequency/nocturia) out of five measured was significantly different between groups in the longer term, being more common among the LDRPB group (LDRPB 25.12% vs DE-EBRT 15.38%, p=0.041). Abugharib et al (2017) found a significant difference in the cumulative incidence of severe GU toxicity at 6 years, (LDRPB 3.6% vs DE-EBRT 1.4%) and 10 years (LDRPB 7.5% vs DE-EBRT 1.4%, p=0.026).

- **Acute gastrointestinal (GI) morbidity** (two studies, n=383, n=320). There was no significant difference between treatment groups in ASCENDE-RT in acute GI morbidity up to 6 months (Rodda et al 2017a). In the LDRPB vs DE-EBRT groups 46.2% vs 45.1% of patients had no symptoms (p=0.961), 39.3% vs 33.3% had mild symptoms (p=0.271), 9% vs 14.3% had moderate symptoms (p=0.090) and none had worse than moderate symptoms. Luo et al (2018) also found no significant difference between the groups, with 88.67% of LDRPB and 90.6% of DE-EBRT patients having no symptoms (p=0.590).
- **Late gastrointestinal (GI) morbidity** (three studies, n=383, n=320, n=579). There was no significant difference between treatment groups in ASCENDE-RT in late GI morbidity up to 5 years after starting pelvic irradiation (Rodda et al 2017a). In the LDRPB vs DE-EBRT groups, 31.3% vs 35.8% of patients had no symptoms (p=0.343), 42% vs 48.2% had mild symptoms (p=0.322), 31.3% vs 20.2% had moderate symptoms (p=0.205) and 8.1% vs 3.2% moderately severe symptoms (p=0.124). The prevalence of late grade ≥3 GI adverse events was 1.7% vs 1.1% at 2 years and 1.0% vs 2.2% at 5 years, with no significant differences between groups (p values not reported). Luo et al (2018) found no difference between treatment groups in five GI symptoms at longer term follow-up. Abugharib (2017) found that the cumulative incidence of moderate or worse GI toxicity in the LDRPB vs DE-BERT groups was 31.2% vs 33.1% at 6 years, and 35.5% vs 33.1% at 10 years, with no significant difference between groups (p=0.45).
- **Erectile function** (one study, n=383). Before starting androgen deprivation therapy (ADT) 63.8% men in the LDRPB group and 61% men in the DE-EBRT group reported adequate erectile function. This declined to 5.2% vs 7.1% one year after starting treatment, recovering to 33.9% vs 30.6% after 5 years, with no significant difference between groups (p=0.60).
- **Median time to first skeletal-related event** (one study, n=320). Median time was significantly longer in those receiving LDRPB (10.4 years (95%CI 8.9-12.2)) compared with DE-EBRT (8.2 years (95%CI 7.1-10.5)), HR 3.361 (95%CI 2.925-3.815), p < 0.001 (Luo et al 2018).
- **Median time to initiation of cytotoxic chemotherapy** (one study, n=320). Median time was significantly longer in those receiving LDRPB (11.6 years (95%CI 9.8-12.7)) compared with DE-EBRT (8.8 years (95%CI 6.3-10.9)), HR 1.627 (95%CI 1.311-1.809), p = 0.007 (Luo et al 2018).
- **Changes in health-related quality of life** (HRQoL) (one study, n=357). Using the SF36v2[6], baseline scores were between 80-90 for most domains (physical function, bodily pain, role physical, social function, role emotional, urinary function), between 70-80 for vitality, general health and mental health, >90 for bowel function, and 58-60 for sexual function. At 12 months from baseline there had been a decline in both treatment groups in all domains except mental health. The decline was significantly greater in the LDRPB

[6] SF36v2 has 36 items organized into 8 scales: physical function, vitality, general health, bodily pain, role physical, social functioning, role emotional, and mental health. Items were also added for urinary function, bowel function, and sexual function. Scales are scored from 0 to 100, with higher scores representing better HRQoL.

group compared with the DE-EBRT group for physical health (p=0.04), vitality (p=0.02), role physical (=0.01), bowel function (p=0.01) and sexual function (p=0.02). For other domains there was no significant difference in score change between treatment groups. The largest decline (LDRPB vs DE-EBRT) was for sexual function (-30.6 vs -23.8), with larger declines also for physical function (-11.6 vs -7.4), role physical (-20.9 vs -13.1), vitality (-12.2 vs -7.4), and bowel function (-12.2 vs -0.1).

At 6 years scores for most domains had improved compared with 12 month scores (except urinary function for both groups). However scores for most domains were still worse than baseline, except for mental health for which scores had improved further in both groups (LDRPB +2.3 vs DE-EBRT +8.3 compared with baseline). The decline in scores was significantly greater in the LDRPB group compared with the DE-EBRT group for physical function (-15.3 vs -6.9, p=0.03) and urinary function (-3.6 vs -0.5, p=0.04). The domains with the greatest decline in scores at 6 years compared with baseline (LDRPB vs DE-EBRT) were physical function (-15.3 vs -6.9), role physical (-15.3 vs -11.4) and sexual function (-19.2 vs -15.1).

Cost-effectiveness

- No relevant studies of costs or cost-effectiveness were identified.

The ASCENDE-RT trial, reported by Morris et al (2017), Rodda et al (2017a) and Rodda et al (2017b), appears to have been a well-conducted RCT whose findings may be regarded as reliable. However it was only powered to detect differences in biochemical progression-free survival. The retrospective studies included in this review (Abugharib et al, 2017; Luo et al, 2018) provide additional information on outcomes and longer follow-up but have a risk of bias related to their retrospective methodology and incompleteness of reporting. In addition, Abugharib et al (2017) only included intermediate risk patients, and Luo et al (2018) used a different classification of risk from the other studies, meaning that the subjects are not directly comparable across studies. The size of the database study by Johnson et al (2017) adds strength to the findings, but there is a risk of bias due to the retrospective methodology, lack of comparability of groups at baseline and limited information about treatment interventions.

3 Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).
- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for PICO).
- The PICO was used to search for relevant publications in the following sources: Medline, Embase and Cochrane library (see section 10 for search strategy).
- The search dates for publications were between 1st January 2008 and 22nd November 2018.
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion.

- Evidence from all included papers was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using National Service Framework for Long term Conditions (NSF-LTC) evidence assessment framework (see section 7).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8).

4 Results

This rapid evidence review identified three papers reporting a single randomised controlled trial (RCT), the ASCENDE-RT trial, which met the inclusion criteria. This trial compared external beam radiotherapy and low dose rate prostate brachytherapy boost (LDRPB) with dose-escalated external beam radiotherapy (DE-EBRT) in 398 patients with intermediate and high risk localised prostate cancer. The brachytherapy dose used (115Gy) was slightly higher than the currently routinely prescribed dose. The three included papers each reported different outcomes from the ASCENDE-RT trial (Morris et al 2017; Rodda et al 2017a; Rodda et al 2017b).

Three further papers were identified for inclusion. Two retrospective studies reported longer-term follow-up of outcomes similar to those reported by Morris et al (2017) and Rodda et al (2017a) in prostate cancer patients treated with LDRPB or DE-EBRT; one study involved high risk patients (Luo et al 2018), the other involved intermediate risk patients (Abugharib et al 2017). One further study, a large database analysis of over 25,000 subjects treated with either LDRPB or DE-EBRT with outcomes reported to seven years, has also been included (Johnson et al 2017).

No relevant studies were identified which reported costs or cost-effectiveness. Full details of the study designs and outcomes are summarised in the evidence table in section 7.

1. **In patients with intermediate or high risk localised prostate cancer what is the clinical effectiveness of adding a low dose rate brachytherapy boost to external beam radiotherapy compared to external beam therapy alone or surgery?**

Clinical outcomes reported included overall survival, biochemical progression-free survival, median time to biochemical progression, metastasis-free survival, prostate cancer-specific survival and local progression-free survival.

Overall survival

Three studies reported overall survival (OS). Morris et al (2017) found no significant difference in OS for patients in ASCENDE-RT randomised to LDRPB compared with DE-EBRT at 5 years (91.3% vs 88.7%), 7 years, (85.7% vs 81.5%) and 9 years (77.9% vs 73.6%) (p=0.293). The large database study by Johnson et al (2017) found greater OS for patients treated with LDRPB compared with DE-EBRT at 7 years (82% vs 73%), which was statistically significant (Hazard Ratio (HR) 0.70 (95%CI 0.64-0.77)). In follow-up up to 15 years, Luo et al (2018) found a statistically significant improvement in OS for treatment with LDRPB compared with DE-EBRT from 7 years onwards, with OS for LDRPB vs DE-EBRT at 7, 10, 12 and 15 years respectively of 98.3% vs 93.4% (p = 0.039), 97.2% vs 87.3% (p = 0.011), 94.5% vs 81.8% (p = 0.003) and 91.4% vs 76.5% (p < 0.001). Median OS was 12.3 years (95%CI 10.6-13.2) for LDRPB and 9.1 years (95%CI 7.5-12.6) for DE-EBRT (HR 6.358 (95% CI 5.733- 6.627)).

Biochemical progression[7]

Two studies reported biochemical progression-free survival (bPFS). Morris et al (2017) found significantly better bPFS in patients randomised to LDRPB compared with DE-EBRT, up to 9 years post-treatment. For LDRPB the proportions of subjects with bPFS (+/- SD) at 5, 7 and 9 years respectively were 88.7% +/- 4.8, 86.2% +/- 5.4 and 83.3% +/- 6.6 compared with 83.8% +/- 5.6, 75.0% +/- 7.2 and 62.4% +/- 9.8 for DE-EBRT (log-rank p<0.001). Abugharib et al (2017) found significantly better bPFS in patients treated with LDRPB up to 10 years. For LDRPB, the proportions with bPFS at 5 and 10 years were 94.1% (95%CI 90.4-97.8) and 91.7% (95%CI 86.8-96.6), compared with 89.2% (95%CI 85.9-92.5) and 75.4% (95%CI 70.1-80.7) for DE-EBRT (p=0.014).

One study reported median time to biochemical progression. In follow-up up to 15 years, Luo et al (2018) found the median time to biochemical progression was 9.8 years (95%CI 8.5-10.7) for patients receiving LDRPB compared with 6.5years (95%CI 4.8-8.1) for DE-EBRT, a statistically significant difference (HR 5.126 (95%CI 4.251-6.306), p < 0.001).

Biochemical failure

One study reported biochemical failure. Morris et al (2017) reported a significantly higher risk of biochemical failure in subjects who were randomised to DE-EBRT compared with those randomised to LDRPB. On multivariable analysis the HR of biochemical failure in those randomised to DE-EBRT vs those randomised to LDRPB was 2.04 (95%CI 1.25-3.33, p=0.004).

Metastasis-free survival

Two studies reported metastasis-free survival (MFS)[8]. In patients randomised to LDRPB vs DE-EBRT Morris et al (2017) found MFS of 88.6% +/- SD 5.6 vs 84.8% +/- SD 7.6 at 9years. Abugharib et al (2017) found distant MFS in patients treated with LDRPB vs DE-EBRT of 95.2% (95%CI 91.7-98.7) vs 98.3% (95%CI 96.9-99.7) at 5years and 95.2% (95%CI 91.7-98.7) vs 95.3% (95%CI 92.8-97.8) at 10 years (p=0.21). While Morris et al (2017) found a slight benefit in the LDRPB group, and Abugharib et al (2017) in the DE-EBRT group, neither finding was statistically significant.

Prostate cancer-specific survival

One study reported prostate cancer-specific survival (PCSS). Morris et al (2017) found no significant difference between treatment arms in PCSS, which at 9 years follow-up was 94.8% +/-SD 4.0 in the LDRPB group, and 92.1% +/-SD 5.6 in the DE-EBRT group.

Local progression-free survival

One study reported local progression-free survival (LPFS)[9]. Abugharib et al (2017) reported LPFS in intermediate risk patients receiving LDRPB vs DE-EBRT as 100.0% (95%CI 100.0-100.0) vs 99.4% (95%CI 98.6-100.0) at 5years, and 100.0% (95%CI 100.0-100.0) vs 94.9% (95%CI 92.2-97.6) at 10years (p=0.042).

[7] Being free of biochemical progression was defined as a PSA level which rose <2 ng/mL above the nadir level for that patient. Morris et al (2017) also included in their definition the absence of any imaging or clinical recurrence and no receipt of any form of secondary treatment for prostate cancer after completion of protocol interventions. Luo et al (2018) also included, for cases with no previous PSA level decrease, a less than 1.25-fold elevation compared to baseline values.

[8] Morris et al (2017) did not define this outcome or describe how metastases were identified. Abugharib et al (2017) stated that distant metastases were confirmed by imaging and/or biopsy.

[9] Local progression was confirmed pathologically.

2. What is the safety of adding a low dose rate brachytherapy boost to external beam radiotherapy in patients with intermediate or high risk localised prostate cancer compared with external beam therapy alone or surgery?

Safety and adverse event outcomes included acute and late genitourinary (GU) and gastrointestinal (GI) morbidity, erectile function, the median time to skeletal-related events and to the initiation of cytotoxic chemotherapy, and changes in health-related quality of life.

Acute genitourinary morbidity

Two studies reported acute genitourinary (GU) morbidity[10]. In the ASCENDE-RT trial, 98% of subjects were reported to have normal urinary control at baseline. Rodda et al (2017a) found that 19.1% of LDRPB patients were symptom-free up to 6 months, compared with 40.5% of DE-EBRT patients (p<0.0001), and that 30.0% of LDRPB patients had moderate (LENTSOMA grade 2) symptoms, compared with 15.8% of DE-EBRT patients (p<0.0001). Luo et al (2018) also found significantly fewer LDRPB than DE-EBRT patients had no (5.42% vs 12.82%, p=0.02) or mild (ABS grade 1) (25.12% vs 48.72%, p=0.000) acute GU symptoms and significantly more LDRPB than DE-EBRT patients had moderate (ABS grade 2) (31.53% vs 20.51%, p=0.034) or moderately severe (ABS grade 3) (23.15% vs 5.13%, p=0.000) acute GU symptoms. There was no significant difference between groups in the proportion of patients with severe (ABS grade 4) symptoms (LDRPB 14.78% vs DE-EBRT 12.82%, p=0.628).

Late genitourinary morbidity

Three studies reported late GU morbidity[11]. Rodda et al (2017a) found that significantly fewer LDRPB than DE-EBRT patients had no late GU symptoms (20.6% vs 29.6%, p=0.003)), and significantly more LDRPB than DE-EBRT patients had moderate (LENTSOMA grade 2) (32.8% vs 20.6%, p=0.002) or moderately severe (LENTSOMA grade 3) (18.4% vs 5.2%, p<0.001) late GU symptoms up to 5 years after starting pelvic irradiation. There was no difference in the incidence of mild or severe symptoms. The prevalence of late grade ≥3 GU adverse events at 2 years was LDRPB 7.0% vs DE-EBRT 1.1% (p=0.005), and at 5 years was LDRPB 8.6% vs DE-EBRT 2.2% (p=0.058). Luo et al (2018) found only one symptom (frequency/nocturia) out of five measured was significantly different between groups in the longer term, being more common among the LDRPB group (LDRPB 25.12% vs DE-EBRT 15.38%, p=0.041), but the timescale was not specified.

Abugharib et al (2017) found a more than two-fold difference in cumulative incidence of severe (CTCAE grade 3) GU toxicity at 6 years, (LDRPB 3.6% vs DE-EBRT 1.4%) and a more than 5-fold difference at 10 years (LDRPB 7.5% vs DE-EBRT 1.4%, p=0.026).

Acute gastrointestinal morbidity

[10] Rodda et al (2017a) used the LENTSOMA scale. Each grade is defined according to specific symptoms, representing 0 (none), 1 (mild), 2 (moderate) 3 (moderately severe) 4 (severe) 5 (toxicity-related death). Luo et al (2018) used the ABS standard: Grade 0, no complication; Grade 1, mild urination burning and frequency, no intervention required; Grade 2, moderate urination burning and frequency, gross haematuria, conservative measures generally effective; Grade 3, severe urination burning and frequency, gross haematuria, requiring active intervention; Grade 4, severe hesitancy or retention, requiring catheterization.

[11] Rodda et al (2017a) used the LENTSOMA scale. Each grade is defined according to specific symptoms, representing 0 (none), 1 (mild), 2 (moderate) 3 (moderately severe) 4 (severe) 5 (toxicity-related death). Luo et al (2018) assessed 5 types of GU symptoms. Abugharib et al (2017) used the NCI Common Terminology Criteria for Adverse Events (CTCAE), summarised as: Grade 1 Mild, intervention not indicated. Grade 2 Moderate; minimal, local or noninvasive intervention indicated; Grade 3 Severe or medically significant but not immediately life-threatening; hospitalisation indicated; Grade 4 Life-threatening consequences; urgent intervention indicated. Grade 5 Death related to AE

Two studies reported acute gastrointestinal (GI) morbidity[12]. Rodda et al (2017a) found no significant difference in acute GI morbidity between the treatment groups up to 6 months. In the LDRPB vs DE-EBRT groups 46.2% vs 45.1% of patients had no symptoms (p=0.961), 39.3% vs 33.3% had mild (LENTSOMA grade 1) symptoms (p=0.271), 9% vs 14.3% had moderate (LENTSOMA grade 2) symptoms (p=0.090) and none had worse than grade 2 symptoms. Luo et al (2018) also found no significant difference between the groups, with 88.67% of LDRPB and 90.6% of DE-EBRT patients having no symptoms (p=0.590).

Late gastrointestinal morbidity
Three studies reported late GI morbidity[13]. Rodda et al (2017a) found no significant difference between treatment groups in late GI morbidity up to 5 years after starting pelvic irradiation. In the LDRPB vs DE-EBRT groups, 31.3% vs 35.8% of patients had no symptoms (p=0.343), 42% vs 48.2% had mild (LENTSOMA grade 1) symptoms (p=0.322), 31.3% vs 20.2% had moderate (LENTSOMA grade 2) symptoms (p=0.205) and 8.1% vs 3.2% moderately severe (LENTSOMA grade 3) symptoms (p=0.124). The prevalence of late grade ≥3 GI adverse events was 1.7% vs 1.1% at 2 years and 1.0% vs 2.2% at 5 years, with no significant differences between groups (p values not reported). Luo et al (2018) found no difference between treatment groups in five GI symptoms at longer term follow-up, but the timescale was not specified.

Abugharib (2017) found that the cumulative incidence of moderate or worse (CTCAE Grade 2+) GI toxicity in the LDRPB vs DE-BERT groups was 31.2% vs 33.1% at 6 years, and 35.5% vs 33.1% at 10 years, with no significant difference between groups (p=0.45).

Erectile function
One study (Rodda et al 2017a) reported erectile function. Before starting androgen deprivation therapy (ADT) 63.8% men in the LDRPB group and 61% men in the DE-EBRT group reported adequate erectile function. This declined to 5.2% vs 7.1% one year after starting treatment, recovering to 33.9% vs 30.6% after 5 years (p=0.60). There was no significant difference between treatment groups.

Median time to first skeletal-related event
One study (Luo et al 2018) reported median time to the occurrence of a first skeletal-related event (SRE). Median time was significantly longer in those receiving LDRPB (10.4yrs (95%CI 8.9-12.2)) compared with DE-EBRT (8.2 years (95%CI 7.1-10.5)), HR 3.361 (95%CI 2.925-3.815), p < 0.001.

Median time to initiation of cytotoxic chemotherapy
One study (Luo et al 2018) reported median time to initiation of cytotoxic chemotherapy. Median time was significantly longer in those receiving LDRPB (11.6 years (95%CI 9.8-12.7)) compared with DE-EBRT (8.8 years (95%CI 6.3-10.9)), HR 1.627 (95%CI 1.311-1.809), p=0.007.

Changes in health-related quality of life
One study (Rodda et al 2017b) reported changes in health-related quality of life (HRQoL), measured using the SF36v2 which measures eight domains of health, wellbeing and function,

[12] Rodda et al (2017a) used the LENTSOMA scale. Each grade is defined according to specific symptoms, representing 0 (none), 1 (mild), 2 (moderate) 3 (moderately severe) 4 (severe) 5 (toxicity-related death). Luo et al (2018) used the RTOG toxicity scoring criteria.

[13] Rodda et al (2017a) used the LENTSOMA scale. Each grade is defined according to specific symptoms, representing 0 (none), 1 (mild), 2 (moderate) 3 (moderately severe) 4 (severe) 5 (toxicity-related death). Luo et al (2018) assessed 5 types of GI symptoms. Abugharib et al (2017) used the NCI Common Terminology Criteria for Adverse Events (CTCAE), summarised as: Grade 1 Mild, intervention not indicated. Grade 2 Moderate; minimal, local or noninvasive intervention indicated; Grade 3 Severe or medically significant but not immediately life-threatening; hospitalisation indicated; Grade 4 Life-threatening consequences; urgent intervention indicated. Grade 5 Death related to AE

together with three additional domains of urinary, bowel and sexual function, each on a scale from 0-100 (higher score indicating better function). Baseline scores were between 80-90 for most domains (physical function, bodily pain, role physical, social function, role emotional, urinary function), between 70-80 for vitality, general health and mental health, >90 for bowel function, and 58-60 for sexual function.

At 12 months from baseline there had been a decline in all domains except mental health (which had increased +0.8 in the LDRPB group and +6.2 in the DE-EBRT group). The decline was significantly greater in the LDRPB group compared with the DE-EBRT group for physical health (p=0.04), vitality (p=0.02), role physical (p=0.01), bowel function (p=0.01) and sexual function (p=0.02). For other domains there was no significant difference in score change between treatment groups. The largest decline (LDRPB vs DE-EBRT) was for sexual function (-30.6 vs -23.8), with larger declines also for physical function (-11.6 vs -7.4), role physical (-20.9 vs -13.1), vitality (-12.2 vs -7.4), and bowel function (-12.2 vs -0.1).

At 6 years, scores for most domains had improved compared with 12 month scores (except urinary function for both groups). However scores for most domains were still worse than baseline, except for mental health for which scores had improved further in both groups (LDRPB +2.3 vs DE-EBRT +8.3 compared with baseline). The decline in scores was significantly greater in the LDRPB group compared with the DE-EBRT group for physical function (-15.3 vs -6.9, p=0.03, p=0.03) and urinary function (-3.6 vs -0.5, p=0.04). The domains with the greatest decline in scores at 6 years compared with baseline (LDRPB vs DE-EBRT) were physical function (-15.3 vs -6.9), role physical (-15.3 vs -11.4) and sexual function (-19.2 vs -15.1).

3. **What is the cost effectiveness of adding a low dose rate brachytherapy boost to external beam radiotherapy in patients with intermediate or high risk localised prostate cancer compared with external beam therapy alone or surgery?**

No relevant studies of costs or cost-effectiveness were identified.

5 Discussion

Three papers reported clinical effectiveness, safety and health-related quality of life (HRQoL) outcomes from the ASCENDE-RT trial, a well-conducted RCT which compared external beam radiotherapy and low dose rate prostate brachytherapy boost (LDRPB) with dose-escalated external beam radiotherapy (DE-EBRT) in 398 patients with intermediate or high risk localised prostate cancer (Morris et al 2017; Rodda et al 2017a; Rodda et al 2017b). The trial included follow-up to a median of 6.5 years but was only powered to detect differences in biochemical progression-free survival at this point. The brachytherapy dose used (115Gy) was slightly higher than the currently routinely prescribed dose and it is not possible to judge how outcomes from current treatment regimes might differ from those reported in this trial.

Two retrospective studies included high or intermediate risk prostate cancer patients treated with LDRPB or DE-EBRT and reported longer-term follow-up of outcomes similar to those reported in ASCENDE-RT (Luo et al 2018; Abugharib et al 2017). These provide additional information on outcomes and longer follow-up but have a risk of bias related to the retrospective methodology and incomplete reporting. In addition, Abugharib et al (2017) only included intermediate risk patients, and Luo et al (2018) used a different classification of risk from the other studies, meaning that the subjects are not directly comparable across studies. A large database analysis of 25,038

subjects with intermediate or high risk prostate cancer treated with either LDRPB or DE-EBRT and overall survival reported to 7 years has also been included (Johnson et al 2017). The size of this study adds strength to the findings, but there is a risk of bias due to the retrospective methodology, lack of comparability of groups at baseline and limited information about treatment interventions.

Biochemical progression of prostate cancer is reflected by changes in prostate-specific antigen (PSA) levels, and is used as an indicator of disease progression. There is good evidence that patients treated with LDRPB are likely to have a longer period after treatment without biochemical progression than patients treated with DE-EBRT. Morris et al (2017), the most reliable study, found that up to 9 years after treatment, 83% of the LDRPB group were free of biochemical progression compared with 62% of the DE-EBRT group. Abugharib et al (2017) found a slightly smaller difference between treatment groups, but with higher overall biochemical progression-free survival at 10 years (92% in the LDRPB group compared with 75% in the DE-EBRT group) which is likely to be related to differences in risk group and methodology. On longer-term follow-up there was a significant difference in median time to biochemical progression, which was 9.8 years for LDRPB patients, compared with 6.5 years for DE-EBRT (Luo et al 2018).

Findings for other clinical effectiveness outcomes differed between studies. The ASCENDE-RT trial found no significant differences between treatment groups in overall survival, metastasis-free survival and prostate cancer-specific survival up to 9 years, although for each measure there was a small, but not statistically significant advantage for LDRPB patients compared with DE-EBRT (Morris et al 2017). The two other studies which reported overall survival found significant improvements for the LDRPB group, at 7 years follow-up in the large database study (Johnson et al 2017), and from 7 years up to 15 years follow-up in the longer-term retrospective study (Luo et al 2018). However due to methodological limitations both these findings should be regarded as only moderately reliable.

The side-effects of radiotherapy can have significant effects on function and quality of life and sometimes be severe or life-threatening. In the ASCENDE-RT trial, 98% of subjects were reported to have normal urinary control at baseline. Six months after starting treatment, the LDRPB group had significantly worse acute genitourinary (GU) morbidity than the DE-EBRT group, with only one-fifth of LDRPB subjects free of GU symptoms compared with two-fifths of the DE-EBRT group, and more LDRPB subjects reporting more severe symptoms (Rodda et al 2017a). A similar finding was reported by Luo et al (2018). While some acute GU symptoms resolve over time or with treatment, significantly more LDRPB patients also had late GU morbidity up to 5 years after treatment; again, around one-fifth were symptom-free compared with around 30% of the DE-EBRT group (Rodda et al 2017a). The two retrospective studies also found significantly more late GU morbidity in patients treated with LDRPB (Luo et al 2018, Abugharib et al 2017).

In contrast, no studies found a significant difference between groups in acute or late gastrointestinal (GI) symptoms. While around two-thirds of all patients reported some symptoms up to 5 years after treatment, almost all were mild or moderate (Rodda et al 2017a). Erectile function after starting androgen deprivation therapy was reported in ASCENDE-RT, which found that 61-64% of men reported adequate erectile function before treatment, declining to only 5-7% after one year and increasing to around half the baseline level at 5 years, with no significant difference between the radiotherapy treatment groups (Rodda et al 2017a).

Health-related quality of life (HRQoL) up to 6 years after starting treatment was also reported in the ASCENDE-RT trial, although reporting of the HRQoL findings was less robust than reporting of other outcomes due to lack of information on measures and numbers included in the analysis

(Rodda et al 2017b). Generally, HRQoL in relation to most areas of physical health and wellbeing had declined a year after starting treatment, with particularly marked declines in measures of sexual and physical function and greater declines for the LDRPB treatment group than the DE-EBRT group. At 6 years scores for most areas had improved compared with the 12 month scores, though most were still worse than baseline, and the LDRPB group still scored significantly worse for physical and urinary function. The exception was the mental health domain, in which subjects' scores improved at 12 months compared with baseline, and improved further at 6 years, particularly in the DE-EBRT group.

Overall, the findings of the studies included in this review suggest that treatment of intermediate or high risk localised prostate cancer with LDRPB may be more clinically effective than treatment with DE-EBRT, but that it also causes increased GU morbidity both in the shorter and longer term, and appears to be associated with a greater decline in some aspects of HRQoL. LDRPB appears to improve biochemical progression-free survival after treatment, and while this may be expected to translate into better overall survival, the evidence supporting an effect on overall survival is from studies which are subject to bias due to their methodology.

The risk profiles of subjects in the included studies were clearly defined and the findings should be generalisable to patient groups with similar characteristics. However, there is insufficient evidence from these studies to judge what the balance between clinical benefit and adverse effects might be for an individual patient undergoing either of the treatments. There was also no evidence on the cost-effectiveness of LDRPB or DE-EBRT.

To provide more conclusive evidence of the benefits and risks associated with LDRPB and DE-EBRT, larger randomised studies would be required which were powered to detect differences in survival, other clinical and safety outcomes, and cost-effectiveness, with long-term follow up. An analysis which considered positive and negative outcomes together would help provide evidence on the balance of benefits and risks. Further research could also usefully compare LDRPB with other treatment options, but no other studies which included other comparators and met the PICO for this review were identified.

6 Conclusion

The best evidence on the clinical effectiveness of external beam radiotherapy and low dose rate prostate brachytherapy boost (LDRPB) compared with dose-escalated external beam radiotherapy (DE-EBRT) for intermediate or high risk localised prostate cancer comes from the ASCENDE-RT trial, which randomised 398 men to either treatment and reported median follow-up for clinical and safety outcomes of 6.5 years. The study was powered to detect differences in biochemical progression-free survival at this time point, and a significant benefit was found for the LDRPB group. However this group also had worse short- and longer-term GU morbidity and greater declines in HRQoL. Three other nonrandomised studies comparing the same treatment interventions in intermediate or high risk patients found other clinical benefits for the LDRPB group, including improved overall survival, but these findings are less reliable due to the design of these studies.

Being free of biochemical progression of prostate cancer is an important outcome for patients, their families and clinicians, as biochemical progression is an indicator of disease progression. The studies included in this review suggest that LDRPB treatment may be associated with improved overall survival, but do not provide conclusive evidence of this. They also provide limited evidence on the likely balance between benefits and risks for patients undergoing either treatment. This information would be extremely important for patients and their clinicians making

a decision about treatment options particularly in view of the evidence on increased morbidity in the LDRPB group. Further well-designed studies are needed to provide evidence on the clinical effectiveness, cost-effectiveness and safety of LDRPB and other treatment options for intermediate or high risk localised prostate cancer.

7 Evidence Summary Table

For abbreviations see list after tables

Dose-escalated external beam radiation therapy boost vs Low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Luo et al 2018	P1 Retrospective analysis of prospectively collected data on 2 treatment cohorts Single institution, China	n=320 high risk n= 117 DE-EBRT n= 203 LDRPB Whole group: median age 70yrs Stage: T2b 7.2% T2c 52.2% T3a 25.6% T3b 15% Gleason score: GS ≤6: 0.9% GS 7: 3.4% GS≥8:95.6% iPSA ≤10: 10.9% 10-20:15.3% ≥20: 73.8%	All treated high risk (Memorial Sloan-Kettering definition) prostate Ca patients were enrolled retrospectively Method of treatment allocation not stated DE-EBRT: 45 Gy of pelvic irradiation, plus DE-EBRT boost to 76~81 Gy	Primary Clinical effectiveness	Overall survival (OS) at 5,7,10,12 and 15 yrs %, DE-EBRT vs LDRPB p value of difference	5yrs: 99.4 vs 96.6%, p = 0.241 7yrs: 98.3 vs 93.4%, p = 0.039 10yrs: 97.2 vs 87.3%, p = 0.011 12yrs: 94.5 vs 81.8%, p = 0.003 15yrs: 91.4 vs76.5% p < 0.001	6	Direct	Subjects in this study were classified as high risk using the following definition: PSA ≥ 20 ng/mL, Gleason score ≥ 8, clinical stage ≥ T2c, and/or two to three intermediate-risk features. It therefore appears that some of them would have been intermediate risk according the NCCN or NICE definitions. The study used retrospective data analysis, and method of treatment allocation was not described so it was not clear how comparable patients in the different treatment groups were at the time of treatment. However there were no statistically significant differences between the treatment groups in a range of risk factors. Follow-up included PSA measurement, and annual radioisotope scan of the bone and computed tomography of the pelvis, lung, and skull. This suggests that ascertainment of skeletal-related events was likely to be accurate. Median follow-up was 90 months (range 12-186 months). Outcomes were reported up to 15 yrs. No details were provided on the number of patients followed up for each outcome. The authors found that the LDRPB group had significantly better OS, longer median time to
				Primary Clinical effectiveness	Median overall survival, yrs (95% CI) Hazard ratio (95% CI)	DE-EBRT: 9.1 (7.5-12.6) LDRPB: 12.3 (10.6-13.2) HR: 6.358 (5.733-6.627) p < 0.001			
				Primary Clinical effectiveness	Median time to biochemical progression[14], yrs (95% CI) Hazard ratio (95% CI)	DE-EBRT: 6.5 (4.8-8.1) LDRPB: 9.8 (8.5-10.7) HR: 5.126 (4.251-6.306) p<0.001			

[14] Defined as a more than 1.25-fold elevation in PSA compared to baseline values (for cases with no previous PSA level decrease) or (for the remaining cases) exceeding the nadir level by ≥ 2 ng/mL

Dose-escalated external beam radiation therapy boost vs Low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		No statistically significant differences between treatment groups.	LDRPB: 45 Gy of pelvic irradiation, plus LDR permanent prostate brachytherapyboost to 110 Gy with I-125 All patients received 36m androgen decrease	Secondary Safety	Median time to first skeletal-related event (SRE)[15], yrs (95% CI) Hazard ratio (95% CI)	DE-EBRT: 8.2 (7.1-10.5) LDRPB: 10.4 (8.9-12.2) HR: 3.361 (2.925-3.815) p < 0.001			biochemical progression, to first SRE, and to initiation of CCT, and fewer acute GU symptoms. This appears to have been a reasonably well conducted study. However the findings can only be viewed as moderately reliable due to the retrospective methodology and lack of details on treatment allocation and data completeness which increase the risk of bias.
				Secondary Clinical effectiveness	Median time to initiation of cytotoxic chemotherapy (CCT), yrs (95% CI) Hazard ratio (95% CI)	DE-EBRT: 8.8 (6.3-10.9) LDRPB: 11.6 (9.8-12.7) HR 1.627 (1.311-1.809) p = 0.007			
				Secondary Safety	Acute urogenital symptoms, ABS grade [16] %, DE-EBRT vs LDRPB, p value	Grade 0 12.82 vs 5.42 p=0.020 Grade 1 48.72 vs 25.12 p=0.000 Grade 2 20.51 vs 31.53 p=0.034 Grade 3 5.13 vs 23.15 p=0.000 Grade 4 12.82 vs 14.78 p=0.628			

[15] Skeletal-related events were: radiotherapy or bone surgery, pathologic bone fractures, spinal cord compression, and antineoplastic treatment changes for bone pain alleviation

[16] Classified according to American Brachytherapy Society (ABS) standard: Grade 0, no complication; Grade 1, mild urination burning and frequency, no intervention required; Grade 2, moderate urination burning and frequency, gross haematuria, conservative measures generally effective; Grade 3, severe urination burning and frequency, gross haematuria, requiring active intervention; Grade 4, severe hesitancy or retention, requiring catheterisation. Timescale of 'acute' not specified.

Dose-escalated external beam radiation therapy boost vs Low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
				Secondary Safety	Late urology function (% with symptom) (timescale not specified) % DE-EBRT vs% LDRPB, p value	Urgent/Incontinence 1.71 vs 1.48 p=0.872 Hesitancy/Retention 1.71 vs 3.45 p=0.365 Gross Haematuria 4.27 vs 6.4 0 p=0.426 Stricture 0 vs 0.49 p=0.447 Frequency/Nocturia 15.38 vs 25.12 p=0.041			
				Secondary Safety	Acute GI function, RTOG grade [17] % DE-EBRT vs % LDRPB, p value	Grade 0 90.6 vs 88.67 p=0.590 Grade 1 5.13 vs 5.91 p=0.769 Grade 2 3.42 vs 3.45 p=1.00 Grade 3 0.85 vs 1.97 p=0.438 Grade 4 0 vs 0			

[17] Classified according to Radiation Therapy Oncology Group (RTOG) toxicity scoring criteria: Grade 0, no complications; Grade 1, symptoms of rectal frequency, urgency, tenesmus or mucoid stool, treated with conservative measures; Grade 2, intermittent rectal bleeding, rectum erythema, requiring active intervention; Grade 3, rectal ulceration and severe bleeding, may require colonoscopy fulguration and blood transfusion; Grade 4, intestinal obstruction or fistula, massive rectal bleeding, needing urgent surgery or vascular support. Timescale of 'acute' not specified.

Dose-escalated external beam radiation therapy boost vs Low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
				Secondary Safety	Late GI function(% with symptom) (timescale not specified) % DE-EBRT vs % LDRPB, p value	Diarrhoea 21.37 vs 13.3 p=0.060 Nausea/Vomiting 7.69 vs 4.93 p=0.313 Abdominal Pain 4.27 vs 3.94 p=0.885 Rectal Bleeding 5.13 vs 10.34 p=0.106 Intestinal Fistula 0 vs 0.49 p=0.447			
Morris et al 2017	P1 RCT (ASCEN DE-RT) Mulitcentre (6 treatment centres, Canada)	n=398 LDRPB n=198 DE-EBRT n=200 Median age 68yrs 69% (n=296) high risk, 31% (n=122) intermediate risk 5.5% had GS6, 54% had GS7, 41% had GS 8-10; 8.8% had iPSA <5, 39% had iPSA 5-10, 33% had iPSA	Patients stratified by risk group (NCCN classification), then randomised to either: Intervention (LDRPB boost) (n=198): 12m ADT, pelvic irradiation to 46Gy, LDRPB boost (^{125}I brachytherapy Implant) (minimal peripheral	Primary Clinical effectiveness	Biochemical progression-free survival[18] (bPFS), % Kaplan-Meier estimates +/- SD	DE-EBRT 5y: 83.8 +/- 5.6 7y: 75.0 +/- 7.2 9y: 62.4 +/- 9.8 LDRPB boost 5y: 88.7 +/- 4.8 7y: 86.2 +/- 5.4 9y: 83.3 +/- 6.6 log-rank p<0.001	9	Direct	Subjects were National Comprehensive Cancer Network (NCCN) high- and intermediate-risk prostate cancer patients (risk groups not defined in this paper but main risk factors described). Allocation was done centrally using computer-generated block randomization with concealed allocation, reducing the risk of bias. There were no significant differences between the treatment arms in a range of baseline and prognostic indicators. The brachytherapy dose used (115Gy) was slightly higher than the currently routinely prescribed dose. It is not possible to judge what impact this may have had on clinical effectiveness outcomes compared with what might be expected from current treatment regimes. There were 29 major protocol violations; 14 involved crossover of patients between treatment groups; 15 involved patients who did not receive either protocol treatment. Analysis was intent-to-treat and no patients were excluded from analysis of the disease control endpoints reported here.
				Primary Clinical effectiveness	Overall survival, (OS), % Kaplan-Meier estimates +/- SD	DE-EBRT 5y: 88.7 +/- 4.8 7y: 81.5 +/- 6.4 9y: 73.6 +/- 8.4 LDRPB boost 5y: 91.3 +/- 4.4 7y: 85.7 +/- 5.8 9y: 77.9 +/- 8.2 log-rank p=0.293			
				Primary Clinical effectiveness	Metastasis-free survival (MFS)[19], %	DE-EBRT 5y: 92.5 +/- 4.0 7y: 92.5 +/- 4.0			

[18] bPFS: defined as the absence of any biochemical (nadir prostate-specific antigen level plus 2 ng/mL threshold), imaging, or clinical recurrence of prostate cancer and no receipt of any form of secondary treatment for prostate cancer after completion of protocol interventions.

[19] Not defined; no further details of how metastases were identified

Dose-escalated external beam radiation therapy boost vs Low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		10-20, 19% had iPSA >20 71% had T1c-T2c tumours, 29% had T3a tumours Details of urinary function not reported No significant differences between treatment groups	dose of 115 Gy) Control (DE-EBRT) (n=200): 12m ADT, pelvic irradiation to 46Gy, DE-EBRT boost of 32Gy in 16 fractions		Kaplan-Meier estimates +/- SD	9y: 84.8 +/- 7.6 LDRPB boost 5y: 93.3 +/- 3.8 7y: 91.0 +/- 4.6 9y: 88.6 +/- 5.6 Difference between treatment arms not reported			Median follow-up at analysis was 6.5 yrs. Baseline appears to have been start of treatment (the first ADT injection) (referred to in figures but not explicitly stated). Overall this appears to have been a well-conducted study whose findings can be viewed as reliable. The study found a significant improvement in bPFS with LDRPB compared with DE-EBRT, but no significant differences in OS, MFS or PCSS. The authors commented that a statistical correlation was found between biochemical failure and increased all-cause mortality (MVA HR 6.30, p<.0.001), but no association between LDRPB and improved OS despite the reduction in biochemical failure with LDRPB. They considered that the lack of effect demonstrated on OS may be due to relatively small study size and short follow-up. However the study appeared only to have been designed to detect differences in bPFS at 6.5 yrs (not in OS or other outcomes). The authors referred to findings in the separate study on toxicity (Rodda et al 2017a) and concluded that incorporating an LDRPB boost, or any method of dose escalation, should be individualised and requires careful consideration of the potential risks and benefits.
				Primary Clinical effectiveness	Prostate cancer-specific survival (PCSS), % Kaplan-Meier estimates +/- SD	DE-EBRT 5y: 97.5 +/-2.4 7y: 94.1 +/- 4.2 9y: 92.1 +/- 5.6 LDRPB boost 5y: 96.8 +/- 2.8 7y: 96.0 +/- 3.2 9y: 94.8 +/- 4.0 No difference between treatment arms (p value not reported)			
				Primary Clinical effectiveness	Biochemical failure Hazard Ratio DE-EBRT vs LDRPB	UVA[20]: HR 2.17, 95% CI 1.33-3.45, p=0.002 MVA[21]: HR 2.04 , 95% CI 1.25-3.33, p=0.004			
				Primary Clinical effectiveness	Overall survival (OS) Hazard Ratio	UVA: HR 1.29, 95% CI 0.80-2.08, p= 0.30 MVA: HR 1.13, 95% CI 0.69-1.84 p=0.62			

[20] UVA: Univariate Cox regression analysis. For the bPFS endpoint, the UVA included age, randomization arm, T stage, GS, iPSA, percentage of positive cores (PPC), NCCN risk stratum, and the number of high-risk features. For OS, biochemical failure status was included as a time-dependent variable.
[21] MVA: Multivariable Cox regression analysis. Variables with P≤.3 on UVA were included in the MVA. The NCCN risk strata and the number of high-risk features were excluded from the MVA models, because they were composites of other variables

Dose-escalated external beam radiation therapy boost vs Low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
					DE-EBRT vs LDRPB				
Rodda et al 2017 (a)	P1 RCT (ASCENDE-RT) Mulitcentre (6 treatment centres, Canada)	Total study population as Morris et al (2017) n=383 subjects. Excluded 15 included in Morris et al (2017) who received neither treatment (7 had been assigned to DE-EBRT, and 8 to LDRPB) n=195 DE-EBRT n=188 LDRPB Median age 68yrs Risk group: 30.7%	Interventions as Morris et al (2017) Subjects were analysed by treatment received. 6 men assigned to EBRT had received LDRPB, and 8 assigned to LDRPB had received DE-EBRT	Primary Safety	Acute genitourinary (GU) morbidity (occurring within 6 months of starting pelvic irradiation) LENTSOMA grade (0-5)[22], % of subjects	0: DE-EBRT 40.5, LDRPB 19.1 1: DE-EBRT 35.8, LDRPB 39.8 2: DE-EBRT 15.8, LDRPB 30.0 3: DE-EBRT 0.5, LDRPB 2.5 4-5: DE-EBRT 0, LDRPB 0 p value of difference 0 <0.0001 1 0.562 2 <0.0001 3 0.121 4-5 N/A	8	Direct	Subject selection and allocation as Morris et al (2017) above. Baseline measures of risk group, IPSS (International Prostate Symptom Score), urinary control and erectile function did not differ between treatment groups. Follow-up was conducted through clinic visits every 4 months for the first year, every 6 months for the next 4 years, and annually thereafter. 15 of the original subjects were excluded because they did not receive either treatment protocol. Fourteen subjects who had been assigned to one treatment group received the other treatment, and analysis was according to treatment received. The protocol specified the method of toxicity data collection, timing of data collection, and the instruments used. However, the trial was powered for the primary endpoint (bPFS), and the plan for toxicity analysis was not specified in the protocol. The brachytherapy dose used (115Gy) was slightly higher than the currently routinely prescribed dose. It is not possible to judge what impact this may have had on toxicity outcomes compared with what might be expected from current treatment regimes.
				Primary Safety	Acute gastrointestinal (GI) morbidity (occurring within 6 months of starting pelvic irradiation) LENTSOMA grade (0-5)[23], % of subjects	0: DE-EBRT 45.1, LDRPB 46.2 1: DE-EBRT 33.3, LDRPB 39.3 2: DE-EBRT 14.3, LDRPB 9.0 3-5: DE-EBRT 0, LDRPB 0 p value of difference 0 0.961 1 0.271 2 0.090 3-5 N/A			

[22] Genitourinary (GU) morbidity was scored using the Late Effects of Normal Tissue - Somatic, Objective, Management, Analytic (LENTSOMA) Scale. Each grade is defined according to specific symptoms, representing 0 (none), 1 (mild), 2 (moderate) 3 (moderately severe) 4 (severe) 5 (toxicity-related death).
[23] Gastrointestinal (GI) morbidity was scored using the Late Effects of Normal Tissue - Somatic, Objective, Management, Analytic (LENTSOMA) Scale. Each grade is defined according to specific symptoms, representing 0 (none), 1 (mild), 2 (moderate) 3 (moderately severe) 4 (severe) 5 (toxicity-related death).

Dose-escalated external beam radiation therapy boost vs Low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		intermediate69.3% high Normal baseline urinary control: 98% Baseline IPSS, median: 6 Erections adequate for penetration: 62.9% No significant differences between treatment groups		Primary Safety	Late GU morbidity (occurring >6 months after starting pelvic irradiation), cumulative incidence Maximum LENTSOMA grade (0-5). 5-year actuarial cumulative incidence, % of subjects	0 DE-EBRT 29.6 LDRPB 20.6 1 43.8 33.7 2 20.6 32.8 3 5.2 18.4 4-5 0.6 2.1 Hazard Ratio (95% CI) 0 0.51 (0.32-0.8) 1 0.75 (0.5401.04) 2 1.97 (1.3-3.0) 3 3.46 (1.7-7.07 4-5 2.05 (0.19-22.6) p value of difference 0 0.003 1 0.088 2 0.002 3 <0.001 4-5 0.559			Overall this appears to have been a well-conducted study whose findings can be viewed as reliable. The authors concluded that increased risk of GU toxicity in patients receiving LDRPB compared with those receiving DE-EBRT may accompany the reductions in treatment failure found in Morris et al (2017) and that patient selection is therefore important.
				Primary Safety	Late GU morbidity (occurring >6 months after starting pelvic irradiation), prevalence at 2 yrs and 5 yrs Prevalence of late grade ≥3 GU adverse events at 2 yrs and 5 yrs	2yrs DE-EBRT 1.1% LDRPB 7.0% p = 0.005 5yrs DE-EBRT 2.2% LDRPB 8.6% p = 0.058			
				Primary Safety	Late GI morbidity (occurring >6 months after starting pelvic irradiation),	0 DE-EBRT 35.8 LDRPB 31.3 1 48.2 42.0 2 20.2 31.3 3 3.2 8.1			

Dose-escalated external beam radiation therapy boost vs Low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
					cumulative incidence Maximum LENTSOMA grade (0-5), 5-year actuarial cumulative incidence, % of subjects	4-5 | 0 | 1.0 Hazard Ratio (95% CI) 0 0.83 (0.56-1.23) 1 0.86 (0.63-1.16) 2 1.33 (0.86-2.08) 3 2.16 (0.81-5.75) 4-5 N/A p value of difference 0 0.343 1 0.322 2 0.205 3 0.124 4-5 N/A			
				Primary Safety	Late GI morbidity (occurring >6 months after starting pelvic irradiation), prevalence at 2 yrs and 5 yrs Prevalence of late grade ≥3 GI adverse events at 2 yrs and 5 yrs	2yrs DE-EBRT 1.1% LDRPB 1.7% 5yrs DE-EBRT 2.2% LDRPB 1.0% Differences not significant			
				Primary Safety	Erectile function % reporting erections adequate for penetration at 1 and 5yrs after starting ADT	Pre-ADT DE-EBRT 61.0 LDR PB 63.8 1 yr DE-EBRT 7.1 LDRPB 5.2 5 yrs DE-EBRT 30.6 LDRPB 33.9 p=0.60			

Dose-escalated external beam radiation therapy boost vs Low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer											
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results			Quality of Evidence Score	Applicability	Critical Appraisal Summary
Rodda et al 2017 (b)	P1 RCT (ASCEN DE-RT) Mulitcentre (6 treatment centres, Canada)	Total study population as Morris et al (2017) n=357 Excluded 41 recruited during feasibility phase of study which did not include HRQoL measurement In paper text: n=177 DE-EBRT n=180 LDRPB In table: n=180 DE-EBRT n=177 LDRPB Baseline GS, %, DE-EBRTvs LDRPB: GS6: 5 vs 4.5	Interventions as Morris et al (2017)	Secondary Health-related quality of life (HRQoL)	Change in SF36v2[24] domain scores from baseline at 12 months. p value of difference between treatment groups (NS = non significant) For domain abbreviations see footnote	Domain, p value Phys p= 0.04 Vital p= 0.02 Gen H NS Bod P NS Role P p= 0.01 Soc NS Role E NS MH NS Urin NS Bowel p= 0.01 Sex F p= 0.02	DE-EBRT -7.4 -7.4 -0.9 -5.9 -13.1 -5.3 -6.0 +6.2 -0.1 -0.1 -23.8	LDRPB -11.6 -12.2 -4.1 -9.5 -20.9 -8.0 -6.2 +0.8 -0.9 -12.2 -30.6	6	Direct	Subject selection and allocation as Morris et al (2017) above. This paper reported findings on n=357 included in Health-related quality of life (HRQoL) assessments. There was inconsistency in reporting of numbers in different treatment groups. The paper abstract and text reported DE-EBRT n=177 and LDRPB n=180. The table of baseline patient characteristics reported DE-EBRT n=180 and LDRPB n=177. There were no significant differences in baseline characteristics between the groups. Analysis was intent-to-treat. 6 men assigned to EBRT had received LDRPB, and 6 assigned to LDRPB had received DE-EBRT. 12 men did not receive either treatment. The brachytherapy dose used (115Gy) was slightly higher than the currently routinely prescribed dose. It is not possible to judge what impact this may have had on HRQoL outcomes compared with what might be expected from current treatment regimes Median follow-up was 6 years. Follow-up was conducted as in Rodda et al (2017a). Subjects were asked to complete SF36v2 questionnaires at each clinic visit, with additional Urinary, Bowel and Sexual function items. Details of these additional items not described.

[24] SF36v2 is a validated 8-scale profile of functional health and well-being scores. It has 36 items organized into 8 scales: physical function (Phys) (10 items), vitality (Vital) (4 items), general health (Gen H) (5 items), bodily pain (Bod P) (2 items), role physical (Role P) (4 items), social functioning (Soc) (2 items), role emotional (Role E) (3 items), and mental health (MH) (5 items). Items were also added for urinary function (Urin) (4 items), bowel function (Bowel) (4 items), and sexual function (Sex F) (6 items). Scales are scored from 0 to 100, with higher scores representing better HRQoL.

Dose-escalated external beam radiation therapy boost vs Low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer										
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results			Quality of Evidence Score	Applicability	Critical Appraisal Summary
		GS7: 53.9 vs 52.5, GS 8-10: 41.1 vs 42.9 Baseline median iPSA (range): DE-EBRT 11.0 (2.7-39.1) LDRPB 10.2 (2.4-40.0) In both groups 71% had T1c-T2c tumours, 29% had T3a tumours No significant differences between groups		Secondary Health-related quality of life (HRQoL)	Change in SF36v2 domain scores from baseline at 72 months. p value of difference between treatment groups (NS = non significant) For domain abbreviations see footnote	Domain, p value Phys p= 0.03 Vital NS Gen H NS Bod P NS Role P NS Soc NS Role E NS MH NS Urin p= 0.04 Bowel NS Sex F NS	DE-EBRT -6.9 -4.3 +0.2 -3.5 -11.4 -1.4 -7.2 +8.3 -0.5 -2.2 -15.1	LDRPB -15.3 -8.1 -5.8 -8.4 -15.3 -7.8 -7.0 +2.3 -3.6 -3.5 -19.2			Baseline response rate was 82.2% in the DE-EBRT arm and 86.4% in the LDRPB arm. Patients had to have completed a baseline HR-QoL survey to be included in the analysis (n included not stated). Response rate for form completion was 82.1% to 95% in the first 4 years of follow-up, and 74.1% to 82.3% in subsequent years, for both groups. Data completeness was 98.3%. Clear rules were followed for missing data. Overall this appears to have been a reasonably well-conducted study whose findings can be viewed as moderately reliable. However HRQoL was not part of the original study design, and it was not powered to detect changes in HRQoL. Details were not provided about the 3 additional scales used to assess urinary, bowel and sexual function. There was a lack of clarity on numbers included in the analysis. Baseline HRQoL scores were: DE-EBRT / LDR PB Physical function 88.5 / 87.4 Vitality 72.5 / 71.4 General health 76.9 / 76.3 Bodily pain 85.0 / 83.3 Role physical 87.2 / 85.5 Social function 90.2 / 89.7 Role emotional 88.9 / 88.1 Mental health 78.8 / 79.5 Urinary function 82.6 / 83.2 Bowel function 93.0 / 92.3 Sexual function 58.0 / 60.5
Abugharib et al 2017	P1 Retrospective analysis of	n=579 intermediate risk (NCCN classification) prostate cancer patients	Method of allocation to treatment group not described	Primary Clinical effectiveness	Biochemical progression free survival (bPFS), % (95% CI)[25]	5yrs DE-EBRT: 89.2 (85.9-92.5) LDRPB: 94.1 (90.4-97.8)			6	Direct	Patients were intermediate risk according to the NCCN classification. The two treatment groups (DE-EBRT and LDRPB) were treated at two different institutions so there may have been other differences in approach between the two besides type of radiotherapy. There were significant

[25] PSA progression was defined as nadir PSA + 2ng/ml.

Dose-escalated external beam radiation therapy boost vs Low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
	prospectively collected data on 2 treatment cohorts Two institutions, USA	treated consecutively at 2 institutions n=388 DE-EBRT n=191 LDRPB Median age 67yrs Significant difference between groups in: Gleason score: DE-EBRT had lower % of higher GS patients, (p=0.025) Baseline PSA: DE-EBRT had higher % of higher PSA score, (p=0.005); Receipt of ADT: 25% of DE-EBRT group vs 36% of LDRPB group had ADT(p=0.008)	DE-EBRT: 77.5 Gy in 1.8-2.0Gy daily fractions LDRPB: 90-108 Gy implant (I^{125} seeds) plus EBRT 45-55.8 Gy in 1.8-2.0 fractions In addition patients in both groups had ADT for 6 months at the treating physicians' discretion Median follow-up 7.5 yrs			10 yrs DE-EBRT: 75.4 (70.1-80.7) LDRPB: 91.7 (86.8-96.6) p=0.014			differences between the groups in Gleason score, baseline PSA and receipt of ADT. Patients were followed up 3-monthly for 2 years, then 6-monthly. Median follow-up was 7.5 years. Metastases were confirmed by imaging and/or biopsy and local recurrences were confirmed pathologically. Numbers followed up at each time point for each measure were provided which suggest that there may have been up to 30% missing data at later time points for bPFS. For LPFS and MFS there appeared to be no more than 4% missing data at any point. The study provides some evidence on longer-term (up to 10 years) outcomes. The authors found better bPFS, LPFS and MFS and less GU toxicity up to 10yrs. However there is a risk of bias due to the retrospective design, lack of information about treatment allocation, lack of comparability of the treatment groups and missing data.
				Primary Clinical effectiveness	Local progression-free survival (LPFS)[26], % (95% CI)	5yrs DE-EBRT: 99.4 (98.6-100.0) LDRPB: 100.0 (100.0-100.0) 10 yrs DE-EBRT: 94.9 (92.2-97.6) LDRPB:100.0 (100.0-100.0) p=0.042			
				Primary Clinical effectiveness	Distant metastasis-free survival (MFS)[27], % (95% CI)	5yrs DE-EBRT: 98.3 (96.9-99.7) LDRPB: 95.2 (91.7-98.7) 10 yrs DE-EBRT: 95.3 (92.8-97.8) LDRPB:95.2 (91.7-98.7) p=0.21			

[26] Local recurrences were confirmed pathologically

[27] Distant metastases were confirmed by imaging and/or biopsy

Dose-escalated external beam radiation therapy boost vs Low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		No significant differences in age, T stage, risk group, length of follow-up		Secondary Safety	Cumulative incidence of Grade 3 GU toxicity[28], %	6yrs DE-EBRT: 1.4% LDRPB: 3.6% 10yrs DE-EBRT: 1.4% LDRPB: 7.5% p=0.026			
				Secondary Safety	Cumulative incidence of Grade 2+ GI toxicity, %	6yrs DE-EBRT: 33.1 LDRPB: 31.2 10yrs DE-EBRT: 33.1 LDRPB: 35.5 p=0.45			
Johnson et al 2017	P1 Retrospective database analysis USA national cancer database	n=25 038 DE-EBRT: n= 20 522 (82%) LDRPB: n=4516 (18%) Inclusion/exclusion criteria mirrored those used in ASCENDE-RT (Morris et al 2017)	Subjects were men in the National Cancer Database (USA), diagnosed between 2004 and 2012 with intermediate- or high-risk prostate cancer	Primary Clinical effectiveness	Overall survival (OS) at 7 yrs, % Hazard ratio, univariate analysis (UVA) (95% CI) Hazard ratio, multivariate analysis (MVA) (95% CI)	DE-EBRT: 73% LDRPB: 82% HR (UVA) 0.63, (0.58–0.68) HR (MVA) 0.70 (0.64-0.77)	6	Direct	This retrospective database analysis included >25,000 men with intermediate or high risk prostate cancer (NCCN classification) treated in USA centres. There was limited detail about the treatment interventions used. There were significant differences between the treatment groups, the LDRPB group being younger and having lower risk and disease progression indicators, and being followed up for longer (median 71m vs 61m). Multivariate analyses (MVA) were carried out using Cox proportional hazards to control for the covariates found to be significant ($p < 0.05$) on univariate analysis (UVA). These included treatment

[28] Toxicity was scored using the Common Terminology Criteria for Adverse Events as defined by the NCI: Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. Grade 3 Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self care ADL. Grade 4 Life-threatening consequences; urgent intervention indicated. Grade 5 Death related to AE. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf

Dose-escalated external beam radiation therapy boost vs Low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		Significant differences between groups included (DE-EBRT vs LDRPB): Median follow-up: 61m vs 71m, p<0.001 Median age: 70 vs 67yrs, p<0.001 High risk: 55% vs 44%, p<0.001 GS: LDRPB had lower GSs, p<0.001 PSA: LDRPB had lower PSA levels, p<0.001 Clinical stage: LDRPB had lower T stage, p<0.001	(NCCN classification) and treated with definitive radiotherapy The database includes hospital registration data from >1500 centres in the USA Treatment groups: LDRPB: EBRT followed by LDRBT DE-EBRT: EBRT followed by DE-EBRT (dose between 75.6-86.4Gy) For both, ADT was started within 8 months before EBRT						type, age, race, insurance type, geographic region, facility type, comorbidity score, GS, PSA, and clinical stage. OS at 7yrs remained significantly better for the LDRPB group on MVA. The size of this database study adds strength to the findings, but due to the lack of comparability at baseline, limited information about treatment interventions used, and retrospective analysis, it is not possible to say whether there remained confounders which were not accounted for.

Dose-escalated external beam radiation therapy boost vs Low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary

Abbreviations

ABS: American Brachytherapy Society; ADT: Androgen deprivation therapy; bPFS: biochemical progression-free survival;BT: Brachytherapy; CI: Confidence Interval; DE-EBRT: dose-escalated external beam radiation therapy; EBRT: external beam radiation therapy; GI: Gastrointestinal; GS: Gleason score; GU: Genitourinary; Gy: Gray; HR: Hazard Ratio; HRQoL: Health-related quality of life; iPSA: pretreatment prostate-specific antigen; IPSS: International Prostate Symptom Score; LDRBT: low dose-rate brachytherapy; LDRPB: low-dose-rate prostate brachytherapy boost; LENTSOMA: Late Effects of Normal Tissue - Somatic, Objective, Management, Analytic; LPFS: Local progression-free survival; m: months; MFS: Metastasis-free survival; MVA: multivariable analysis; NCCN: National comprehensive cancer network; NCI: National Cancer Institute; OS: Overall Survival; PCSS: prostate cancer-specific survival; PSA: Prostate-specific antigen; RTOG: Radiotherapy oncology group; UVA: Univariate analysis

8 Grade of Evidence Table

For abbreviations see list after tables

Dose-escalated external beam radiation therapy boost vs Low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Overall survival (OS)	Morris 2017	9	Direct	A	Overall survival is the proportion of patients still alive at a defined time point after baseline. Morris et al found no significant difference in OS for patients randomised to LDRPB compared with DE-EBRT at 5 years (91.3% vs 88.7%), 7 yrs (85.7% vs 81.5%) and 9yrs (77.9% vs 73.6%) after starting ADT (log-rank p=0.293). Overall survival is an extremely important outcome for patients, their families and clinicians. A gain in overall survival would extend the lives of patients. There was no statistically significant difference in OS between patients randomised to LDRPB compared with DE-EBRT. The most reliable study (Morris et al) found no statistically significant difference in OS between LDRPB and DE-EBRT, but the study was not powered to detect differences in OS. This was a well-conducted RCT and the findings can be regarded as reliable.
	Luo 2018	7	Direct		
	Johnson 2017	6	Direct		
Prostate cancer-specific survival (PCSS)	Morris 2017	9	Direct	B	Prostate cancer-specific survival is the proportion of people who have not died from prostate cancer in a defined period of time, for example between date of diagnosis or date or first treatment and death; the term was not further defined by Morris et al. Deaths were classified as being due to prostate cancer if this was identified as the cause of death, or if men were recorded as having been treated with systemic agents for metastatic prostate cancer at or before their death, regardless of the proximate cause of death. Morris et al found no significant difference between treatment arms in PCSS, which at 9 years follow-up was 94.8% +/-SD 4.0 in the LDRPB group, and 92.1% +/-SD 5.6 in the DE-EBRT group. Avoiding death due to prostate cancer is an extremely important outcome for patients, their families and clinicians. This study found that treatment with LDRPB was associated with the same risk of death due to prostate cancer as treatment with DE-EBRT. Morris et al was a well-conducted RCT and the findings are likely to be reliable. However the study was not powered to detect differences in PCSS.
Biochemical progression-free survival (bPFS), %	Morris 2017	9	Direct	B	Biochemical progression-free survival is the percentage of people who are alive and free of biochemical progression in a defined period of time. Being free of biochemical progression was defined as a PSA level which rose <2 ng/mL above the nadir level for that patient. Morris et al also included in their definition the absence of any imaging or clinical recurrence and no receipt of any form of secondary treatment for prostate cancer after completion of protocol interventions. Morris et al found significantly better bPFS in patients randomised to LDRPB compared with DE-EBRT, up to 9 years post-treatment. For LDRPB the % bPFS (+/- SD) at 5, 7 and 9 years was 88.7 +/- 4.8, 86.2 +/- 5.4 and 83.3 +/- 6.6 respectively compared with 83.8 +/- 5.6, 75.0 +/- 7.2 and 62.4 +/- 9.8 respectively for DE-EBRT (log-rank p<0.001).
	Abugharib 2017	6	Direct		

Dose-escalated external beam radiation therapy boost vs Low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					Biochemical progression is an important outcome for patients, their families and clinicians as it relates to progression of prostate cancer. Around 20% fewer patients randomised to LDRPB had biochemical progression of disease 9 years after treatment compared with those randomised to DE-EBRT. This was a well-conducted RCT and the findings can be regarded as reliable. The brachytherapy dose used (115Gy) was slightly higher than the currently routinely prescribed dose. It is not possible to judge what impact this may have had on bPFS compared with what might be expected from current treatment regimes
Biochemical failure	Morris 2017	9	Direct	B	Biochemical failure was defined as a PSA level which rose ≥2 ng/mL above the nadir level for that patient. Morris et al found that patients randomised to LDRPB were significantly less likely to experience biochemical failure than those randomised to DE-EBRT. On multivariable analysis (MVA) the hazard ratio (HR) of the difference was 2.04, 95% CI 1.25-3.33, p=0.004. Biochemical failure is an important outcome for patients, their families and clinicians as it relates to progression of prostate cancer. Patients randomised to LDRPB had about half the risk of biochemical failure of those randomised to DE-EBRT. This study suggests that patients randomised to LDRPB were around half as likely to experience biochemical failure as those randomised to DE-EBRT. This was a well-conducted RCT and the findings can be regarded as reliable. The brachytherapy dose used (115Gy) was slightly higher than the currently routinely prescribed dose. It is not possible to judge what impact this may have had on biochemical failure compared with what might be expected from current treatment regimes
Median time to biochemical progression	Luo 2018	7	Direct	B	Median time to biochemical progression was defined as the time taken for the PSA level to rise ≥2 ng/mL above the nadir level for patients in the study population, or (for cases with no previous PSA level decrease), a more than 1.25-fold elevation compared to baseline values. Luo et al reported that, in follow-up to 15 years, the median time to biochemical progression was 9.8 yrs (95%CI 8.5-10.7) for patients receiving LDRPB compared with 6.5yrs (95%CI 4.8-8.1) for DE-EBRT, a significant difference (HR: 5.126,(95% CI 4.251-6.306), $p < 0.001$). Biochemical progression is an important outcome for patients, their families and clinicians as it relates to progression of prostate cancer. Patients receiving LDRPB experienced biochemical progression more than 3 years later on average than those receiving DE-EBRT. This can be regarded as moderately reliable as it is based on a retrospective data review in which treatment groups appeared comparable but which lacked details on treatment allocation and data completeness which increase the risk of bias.

Dose-escalated external beam radiation therapy boost vs Low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Metastasis-free survival (MFS)	Morris 2017	9	Direct	B	Metastasis-free survival is the proportion of people alive who have not developed a metastasis in a defined period of time. Morris et al did not provide details of how metastases were determined. Morris et al found no significant difference in MFS between treatment groups. In patients randomised to LRDPB vs DE-EBRT, MFS was 88.6% +/- SD 5.6 vs 84.8% +/- SD 7.6 at 9yrs. Survival without metastases is extremely important to patients, their families and clinicians as metastases indicate disease progression and may be associated with increased morbidity. This study found that patients treated with LDRPB were likely to live for the same length of time without the development of metastatic disease as those treated with DE-EBRT.. Morris et al was a well-conducted RCT and the findings can be regarded as reliable. However the study was not powered to detect differences in MFS.
	Abugharib 2017	6	Direct		
Local progression-free survival (LPFS)	Abugharib 2017	6	Direct	C	Local progression-free survival is the proportion of people alive without local progression of disease. Local progression was confirmed pathologically. In Abugharib et al, LPFS at 5yrs was 100.0% (95%CI 100.0-100.0) in the LDRPB group and 99.4% (95%CI 98.6-100.0) in the DE-EBRT group , and at 10 yrs was 100.0% (95% CI 100.0-100.0) in the LDRPB group and 94.9% (95%CI 92.2-97.6) in the DE-EBRT (p=0.042). Avoiding local progression of disease is an important outcome for patients, their families and clinicians. Ten years after treatment, no patient receiving LDRPB had experienced local progression of disease while around 5% of those receiving DE-EBRT had done so. This finding can be regarded as only moderately reliable, as this was a retrospective analysis with significant differences between treatment groups, and included only intermediate risk patients.
Median time to first skeletal-related event (SRE)	Luo 2018	7	Direct	B	Median time to first SRE is the median time to presentation of first SRE amongst people in the study population. SREs were defined as radiotherapy or bone surgery, pathologic bone fractures, spinal cord compression, and antineoplastic treatment changes for bone pain alleviation. Patients underwent annual radioisotope scan of the bone and computed tomography of the pelvis, lung, and skull, which suggests that ascertainment of SREs was likely to be accurate. Median time to first SRE was significantly longer in those receiving LDRPB (10.4 yrs (95% CI 8.9-12.2)) compared with DE-EBRT (8.2 yrs (95% CI 7.1-10.5)), HR 3.361 (95% CI 2.925-3.815), p < 0.001. Skeletal-related events are important outcomes for patients, their families and clinicians as they are likely to be related to progression of prostate cancer and may cause significant morbidity. Patients receiving LDRPB experienced their first skeletal-related event more than 2 years later on average than those receiving DE-EBRT, and this difference was statistically significant. This finding is moderately reliable as it is based on a retrospective data review in which treatment groups appeared comparable but which lacked details on treatment allocation and data completeness

Dose-escalated external beam radiation therapy boost vs Low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					which increase the risk of bias. The patients in this study were stated to be high risk but appear to be both intermediate and high risk according to the NCCN classification used in other studies.
Median time to cytotoxic chemotherapy (CCT)	Luo 2018	7	Direct	B	Median time to cytotoxic chemotherapy is the median time between baseline and commencement of cytotoxic chemotherapy amongst people within the study population. Time to commencement of cytotoxic chemotherapy was identified retrospectively from patient records. Luo et al (2018) reported that median time was significantly longer in those receiving LDRPB (11.6 yrs (95% CI 9.8-12.7)) compared with DE-EBRT (8.8 yrs (95% CI 6.3-10.9)), HR 1.627 (95% CI 1.311-1.809), p = 0.007. Not requiring cytotoxic chemotherapy is an important outcome for patients, their families and clinicians as chemotherapy would be required for progression of prostate (or other) cancer and is likely to be associated with significant morbidity. Patients receiving LDRPB commenced cytotoxic chemotherapy almost 3 years later on average than those receiving DE-EBRT, and this difference was statistically significant. This finding is moderately reliable as it is based on a retrospective data review in which treatment groups appeared comparable but which lacked details on treatment allocation and data completeness which increase the risk of bias. The patients in this study were stated to be high risk but appear to be both intermediate and high risk according to the NCCN classification used in other studies.
Acute genitourinary (GU) morbidity	Rodda (2017a)	8	Direct	A	Acute genitourinary morbidity refers to the proportion of people who had early onset GU symptoms. Rodda et al (2017a) scored GU morbidity using the LENTSOMA Scale. Each grade is defined according to specific symptoms, representing 1 (mild), 2 (moderate) 3 (moderately severe) 4 (severe) 5 (toxicity-related death). The maximum LENTSOMA score up to 6 months after starting pelvic irradiation was recorded as acute morbidity. Rodda et al found that up to 6 months after starting radiotherapy, 19.1% of LDRPB patients were symptom-free, compared with 40.5% of DE-EBRT patients (p<0.0001), and 30.0% of LDRPB patients had moderate symptoms, compared with 15.8% of DE-EBRT patients (p<0.0001).There was no difference between groups in the proportions with mild or moderately severe symptoms. Acute GU morbidity is an important outcome for patients, their families and clinicians. While many symptoms resolve over time or with treatment, they can seriously impair quality of life and require further interventions. Half as many LDRPB patients were free of acute GU symptoms compared with DE-EBRT patients, and twice as many LDRPB patients had moderate acute GU symptoms compared with DE-EBRT patients. Rodda et al (2017a) was a well-designed RCT whose findings are likely to be reliable. The brachytherapy dose used (115Gy) was slightly higher than the currently routinely prescribed dose. It is not possible to judge what impact this may have had on acute GU morbidity compared with what might be expected from current treatment regimes. Avoiding acute GU symptoms would be important for patients, though would need to be weighed against the risk of other outcomes such as longer-term morbidity and mortality.
	Luo 2018	7	Direct		

Dose-escalated external beam radiation therapy boost vs Low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Late GU morbidity	Rodda (2017a)	8	Direct	A	Late genitourinary morbidity refers to the proportion of people who had late onset GU symptoms Rodda et al (2017a) scored GU morbidity using the LENTSOMA Scale. Each grade is defined according to specific symptoms, representing 1 (mild), 2 (moderate) 3 (moderately severe) 4 (severe) 5 (toxicity-related death). The cumulative incidence of each maximum LENTSOMA score more than 6 month and up to 5 years after starting pelvic irradiation was recorded as late morbidity.. Rodda et al found that significantly more DE-EBRT patients had no late GU symptoms (LDRPB vs DE-EBRT: 20.6% vs 29.6%, p=0.003), and significantly more LDRPB patients had moderate (32.8% vs 20.6%, p=0.002) or moderately severe (18.4% vs 5.2%, p<0.001) late GU symptoms up to 5 yrs after starting pelvic irradiation. The prevalence of late grade ≥3 GU adverse events at 2 yrs was LDRPB 7.0% vs DE-EBRT 1.1% (p=0.005), and at 5 yrs was LDRPB 8.6% vs DE-EBRT 2.2% (p=0.058). Late GU morbidity is an important outcome for patients, their families and clinicians as it can seriously impair longer-term quality of life and may require further interventions. Patients treated with LDRPB were one-third less likely to be free of late GU symptoms, 50% more likely to have moderate late GU symptoms and three times more likely to have moderately severe late GU symptoms compared with patients treated with DE-EBRT. Rodda et al was a well-designed RCT whose findings are likely to be reliable. The brachytherapy dose used (115Gy) was slightly higher than the currently routinely prescribed dose. It is not possible to judge what impact this may have had on late GU morbidity compared with what might be expected from current treatment regimes. Avoiding late GU morbidity would be important for patients, and would need to be weighed against the risk of other outcomes such as mortality.
	Luo 2018	7	Direct		
	Abugharib 2017	6	Direct		
Acute gastrointestinal (GI) morbidity	Rodda (2017a)	8	Direct	A	Acute gastrointestinal morbidity refers to the proportion of people who had early onset GI symptoms. Rodda et al (2017a) scored GI morbidity using the LENTSOMA Scale. Each grade is defined according to specific symptoms, representing 1 (mild), 2 (moderate) 3 (moderately severe) 4 (severe) 5 (toxicity-related death). The maximum LENTSOMA score up to 6 months after starting pelvic irradiation was recorded as acute morbidity. Rodda et al found no statistically significant difference in acute GI morbidity between the treatment groups. In the LDRPB vs DE-EBRT groups 46.2% vs 45.1% of patients had no symptoms, 39.3% vs 33.3% had grade 1 symptoms, 9% vs 14.3% had grade 2 symptoms and none had worse than Grade 2 symptoms. Acute GI morbidity is an important outcome for patients, their families and clinicians. While symptoms may resolve over time or with treatment, they can seriously impair quality of life and may require further interventions. There was no difference in acute GI morbidity between patients receiving LDRPB compared with DE-EBRT. Rodda et al was a well-designed RCT whose findings are likely to be reliable. Avoiding acute GI symptoms would be important for patients, though would need to be weighed against the risk of other outcomes such as longer-term morbidity and mortality.
	Luo (2018)	7	Direct		
Late GI morbidity	Rodda (2017a)	8	Direct	A	Late gastrointestinal morbidity refers to the proportion of people who had late onset GI symptoms Rodda et al (2017a) scored GI morbidity using the LENTSOMA Scale. Each grade is defined according to specific symptoms, representing 1 (mild), 2 (moderate) 3 (moderately severe) 4 (severe) 5 (toxicity-
	Luo (2018)	7	Direct		
	Abugharib 2017	6	Direct		

Dose-escalated external beam radiation therapy boost vs Low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					related death). The cumulative incidence of each maximum LENTSOMA score more than 6 months and up to 5 years after starting pelvic irradiation was recorded as late morbidity. Rodda et al found no statistically significant difference between treatment groups in late GI morbidity. In the LDRPB vs DE-EBRT groups, 31.3% vs 35.8% of patients had no symptoms, 42% vs 48.2% had mild symptoms, 31.3% vs 20.2% had moderate and 8.1% vs 3.2% moderately severe symptoms. The prevalence of late grade ≥3 GI adverse events was 1.7% vs 1.1% at 2 yrs and 1.0% vs 2.2% at 5 yrs, with no significant differences between groups. Late GI morbidity is an important outcome for patients, their families and clinicians as it can seriously impair longer-term quality of life and may require further interventions. There was no difference in late GI morbidity between patients receiving LDRPB compared with DE-EBRT. Rodda et al was a well-designed RCT whose findings are likely to be reliable. Avoiding late GI morbidity would be important for patients, and would need to be weighed against the risk of other outcomes such as mortality.
Erectile function	Rodda (2017a)	8	Direct	B	Erectile function was defined as the proportion of patients reporting erections adequate for penetration at 1 and 5yrs after starting ADT. In Rodda et al (2017a), 63.8% men in the LDRPB group and 61% men in the DE-EBRT group reported adequate erectile function before treatment. This declined to 5.2% vs 7.1% one year after starting treatment, recovering to 33.9% vs 30.6% after 5 yrs. There was no statistically significant difference between treatment groups. Erectile function is an important outcome for quality of life for patients and their partners. Rodda et al found that about 50% of men who had adequate erectile function before treatment reported having lost it after 5 yrs, regardless of type of radiotherapy, with no differences between treatment groups. This study was well-conducted but this finding is based on a self-reported measure therefore may be subject to bias.
Health-related quality of life (HRQoL)	Rodda (2017b)	6	Direct	B	HRQoL was measured using the SF36v2, a validated 8-scale profile of functional health and well-being scores. It has 36 items organized into 8 scales: physical function, vitality, general health, bodily pain, role physical, social functioning, role emotional, and mental health. Items were also added for urinary function, bowel function, and sexual function. Scales are scored from 0 to 100, with higher scores representing better HRQoL Patients were asked to complete the HRQoL measure at each clinic visit. Rodda et al (2017b) reported change in SF36v2 domain scores from baseline at 12 months and up to 6 years. Baseline scores were between 80-90 for most domains (physical function, bodily pain, role physical, social function, role emotional, urinary function), between 70-80 for vitality, general health and mental health, >90 for bowel function, and 58-60 for sexual function. At 12 months there had been a decline in all domains except mental health (which had increased +0.8 in the LDRPB group and +6.2 in the DE-EBRT group). The decline was significantly greater in the LDRPB group compared with the DE-EBRT group for physical health (p=0.04), vitality (p=0.02), role physical (p=0.01), bowel function (p=0.01) and sexual function (p=0.02). For other domains there was no significant difference in score

Dose-escalated external beam radiation therapy boost vs Low dose rate brachytherapy boost to treat intermediate or high risk prostate cancer					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					change between treatment groups. The largest decline (LDRPB vs DE-EBRT) was for sexual function (-30.6 vs -23.8), with larger declines also for physical function (-11.6 vs -7.4), role physical (-20.9 vs -13.1) and vitality (-12.2 vs -7.4), and bowel function (-12.2 vs -0.1). At 6 yrs scores for most domains had improved compared with 12 month scores (except urinary function for both groups). However scores for most domains were still worse than baseline, except for mental health for which scores had improved further in both groups (LDRPB +2.3 vs DE-EBRT +8.3). The decline in scores was significantly greater in the LDRPB group compared with the DE-EBRT group for physical function and urinary function. The domains with the greatest decline in scores at 6 years (LDRPB vs DE-EBRT) were physical function (-15.3 vs -6.9), role physical (-15.3 vs -11.4) and sexual function (-19.2 vs -15.1). HRQoL is an extremely important outcome for patients, their families and clinicians. The largest declines in physical, social and general health measures of HRQoL at 12 months after treatment were in domains relating to sexual function, physical function and vitality. Declines were significantly worse in the LDRPB treatment group than the DE-EBRT group for domains relating to physical health, vitality, role physical, bowel function and sexual function. At 6 years after treatment most scores had improved but HRQOL remained worse than at baseline for most areas which were measured, particularly for physical function, role physical and sexual function, and declines remained significantly greater in the LDRPB group for physical function and urinary function. Scores improved in the mental health domain at both 12 months and 6 years in both groups. This analysis was carried out as part of a well-conducted RCT, although was not one of the originally planned analyses. The numbers included in HRQoL measures were not stated, but based on baseline and later response rates provided were likely to be 67-81% patients in the first 4 years, and 60-70% subsequently. There was no information comparing patients included and excluded from the analysis. Data completeness was high at 98.3% and clear rules were followed for missing data. The findings appear to be moderately reliable, and suggest that most measures of HRQoL decline both in the shorter and longer term after treatment with both LDRPB and DE-EBRT, but declines in some domains particularly relating to physical health and functions are greater for the LDRPB group. Conversely, a measure of Mental Health improved for both groups, but particularly the DE-EBRT group. The brachytherapy dose used (115Gy) was slightly higher than the currently routinely prescribed dose. It is not possible to judge what impact this may have had on HRQoL outcomes compared with what might be expected from current treatment regimes. Understanding the risk of decline in HRQoL would be important for patients, and would need to be weighed against the risk of other outcomes such as mortality.

Abbreviations

ABS: American Brachytherapy Society; ADT: Androgen deprivation therapy; bPFS: biochemical progression-free survival;BT: Brachytherapy; CI: Confidence Interval; DE-EBRT: dose-escalated external beam radiation therapy; EBRT: external beam radiation therapy; GI: Gastrointestinal; GS: Gleason score; GU: Genitourinary; Gy: Gray; HR: Hazard Ratio; HRQoL: Health-related quality of life; iPSA: pretreatment prostate-specific antigen; IPSS: International Prostate Symptom Score; LDRBT: low dose-rate brachytherapy; LDRPB: low-dose-rate prostate brachytherapy boost; LENTSOMA: Late Effects of Normal Tissue - Somatic, Objective, Management, Analytic; LPFS: Local progression-free survival; m: months; MFS: Metastasis-free survival; MVA: multivariable analysis; NCCN: National comprehensive cancer network; NCI: National Cancer Institute; OS: Overall Survival; PCSS: prostate cancer-specific survival; PSA: Prostate-specific antigen; RTOG: Radiotherapy oncology group; UVA: Univariate analysis

9 Literature Search Terms

PICO Table	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Patients who have intermediate or high risk localized prostate cancer with adequate urinary function, who are suitable for a general/spinal anaesthetic [High risk = at least one of: PSA≥20, Gleason≥8 or T stage≥T3. Intermediate risk = at least one of: PSA 10-20, Gleason 7, T2b/c.] [Adequate urinary function can be defined by IPSS score<16, urinary maximal flow rate of >15ml/second and post void residual volume of <60ml]
I – Intervention Which intervention, treatment or approach should be used?	LDR brachytherapy to prostate in combination with external beam radiotherapy to prostate +/- pelvic lymph nodes with or without androgen deprivation therapy
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Surgery (robotic assisted, laparascopic or open) OR External beam radiotherapy to prostate +/- androgen deprivation therapy +/- external beam radiotherapy to pelvic lymph nodes OR LDR brachytherapy alone (for selected intermediate risk patients)
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission	*Critical to decision-making:* *Biochemical failure (e.g. ASTRO or Phoenix definition)* *Overall survival* *Prostate cancer specific survival* *Adverse effects (e.g. acute and late urinary toxicity (catheter, urinary retention, incontinence, nocturia); acute and late bowel toxicity, erectile dysfunction; anaesthetic risks; secondary malignancy* *Quality of life (for example, NEI-VFQ-25)* *Important to decision-making:* *Cost effectiveness*
Assumptions / limits applied to search	
Inclusion Criteria	Peer reviewed articles published in journals Language – English only Time frame – studies published in the last 10 years (including 2008) Meta-analyses or controlled studies preferable to cohort studies or case series
Exclusion Criteria	Low risk prostate cancer Definite metastases to lymph nodes or other organs radiologically or on biopsy Publication type: conference abstracts, narrative reviews, commentaries, editorials and case reports

10 Search Strategy

We searched PubMed, Embase and Cochrane Library limiting the search to papers published in England from 1st January 2008 to 22nd November 2018. We excluded conference abstracts, commentaries, letters, editorials and case reports.

Search date: 22 November 2018

Search strategy for Medline and Embase:

1	exp Prostatic Neoplasms/
2	(prostat* adj3 (cancer? or neoplas* or carcinoma? or tumour? or tumor? or malignan*)).ti,ab.
3	1 or 2
4	*brachytherapy/ and radiotherapy dosage/
5	(radiotherapy/ or exp Prostatic Neoplasms/rt) and *brachytherapy/
6	*brachytherapy/ and (low dos* or high dos* or ldr* or hdr*).ti,ab.
7	((external beam or external radi* or radiotherap* or radiation therap* or ert or ebrt) adj5 brachytherap*).ti,ab.
8	((external beam or external radi* or radiotherap* or radiation therap* or ert or ebrt) and brachytherap*).ti.
9	(brachytherap* and boost*).ti,ab.
10	(brachytherap* adj5 (low dos* or high dos* or ldr* or hdr*)).ti,ab.
11	(brachytherap* and (low dos* or high dos* or ldr* or hdr*)).ti.
12	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13	3 and 12
14	PRACTICE GUIDELINE/
15	13 and 14
16	limit 13 to "reviews (maximizes specificity)"
17	(comment or editorial or letter or news or "review").pt. or case report.ti.
18	13 not 17
19	15 or 16 or 18
20	limit 19 to (english language and yr="2008 -Current")
21	exp animals/ not humans.sh.
22	20 not 21

11 Evidence Selection

- Total number of publications reviewed: 171
- Total number of publications considered relevant: 43
- Total number of publications selected for inclusion in this briefing: 6

References from the PWG supplied in the PPP		Paper selection decision and rationale if excluded
1	Morris W.J., Tyldesley, S., Pai, H.H., Halperin, R., McKenzie, M., Duncan, G., Morton, G., Murray, N. & Hamm J. 2015. ASCENDE-RT: A multicenter, randomized trial of dose-escalated external beam radiotherapy (EBRT-B) versus low-dose-rate brachytherapy (LDR-B) for men with unfavourable-risk localized prostate cancer. *Journal of Clinical Oncology*. 33:7_suppl, 3-3.	Excluded. Conference abstract

2	Hoskin, P., Rojas, A., Bownes, P., Lowe, G., Ostler, P. and Bryant, L. 2012. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. *Radiotherapy and Oncology.* 103(2): 217-222.	Excluded. Involves HDRPB not LDRPB so is out of scope of PICO for this review
3	Chin J., Rumble R.B., Kollmeier M., Heath E., Efstathiou J., Dorff T., Berman B., Feifer A., Jacques A & Loblaw D.A. 2017. Brachytherapy for Patients With Prostate Cancer: American Society of Clinical Oncology/Cancer Care Ontario Joint Guideline Update. *Journal of Clinical Oncology*. 35(15): 1737-1745	Excluded. Only one RCT in this systematic review involved LDRPB and has been included in this review (Morris et al 2017).

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NICE 2014a. Prostate cancer: diagnosis and treatment. Full guideline. https://www.nice.org.uk/guidance/cg175/evidence/full-guideline-pdf-191710765 accessed 3/1/2019

NICE 2014b. Prostate Cancer: diagnosis and management. CG 175 https://www.nice.org.uk/guidance/cg175 accessed 30/11/2018

NICE 2005. Low dose rate brachytherapy for localised prostate cancer. IPG 132 https://www.nice.org.uk/guidance/ipg132 accessed 30/11/18.

Rodda S, Tyldesley S, Morris WJ, Keyes M, Halperin R, Pai H, McKenzie M, Duncan G, Morton G, Hamm J, Murray N. 2017(a). 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-

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