NHS England

# Evidence review: High dose rate 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 (IPG 174) on high dose rate brachytherapy in combination with external-beam radiotherapy for localised prostate cancer, published in 2006, stated that 'current evidence on the safety and efficacy of high dose rate (HDR)

[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).

brachytherapy in combination with external-beam radiotherapy for localised prostate cancer appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance' (NICE 2006).

**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)**

- High dose rate brachytherapy (HDRBT) is a form of radiotherapy in which a high dose short-term radiation boost is targeted directly to the prostate gland.

- HDRBT involves transrectal ultrasound (TRUS) guided insertion of needles into the prostate and the passing of a single high activity radiation source along the length of each needle. The needles and radiation source are removed on completion of the procedure.
- Low dose rate brachytherapy (LDRBT) involves the TRUS guided permanent implantation of small radioactive pellets into the prostate gland.
- Both procedures are carried out under spinal or general anaesthetic, and may be carried out as a day-case or an overnight stay in hospital.

**Rationale for use**

- The aim of high dose rate brachytherapy 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

- Seven studies were included in this review comparing high dose rate brachytherapy boost plus EBRT (HDRPB) with other in-scope treatment approaches for intermediate and high risk localised prostate cancer. Two were randomised controlled trials (RCTs) (Hoskin et al, 2102; Lennernas et al, 2015), four were retrospective controlled studies (Wedde et al, 2018; Kishan et al, 2017; Khor et al, 2013; Noda et al, 2011) and one was a cost-effectiveness analysis (Vu et al, 2018).
- In four studies the comparator was external beam radiotherapy (EBRT) (Hoskin et al, 2102; Wedde et al, 2018; Khor et al, 2013; Vu et al, 2018), in two studies the comparator was radical prostatectomy (RP) (Lennernas et al, 2015; Noda et al, 2011) and in one comparators were both EBRT and RP (Kishan et al, 2017).

**Clinical effectiveness**

**High dose rate brachytherapy boost with EBRT versus EBRT alone**

- **Overall survival** (OS). (One study, n=216). OS at 5, 7 and 10 years respectively was 88%, 81% and 67% in the group receiving HDRPB and 89%, 88% and 79% in those receiving EBRT (p=0.2) (Hoskin et al, 2012).
- **Overall mortality** (OM). (One study, n=621). OM at 10 years was 12.92% (42/325) in the group receiving HDRPB and 23.31% (69/296) in the group receiving EBRT alone (p=0.02) (Wedde et al, 2018).
- **Prostate cancer-specific mortality** (PCSM). (One study, n=621). PCSM at 5 and 10 years was 1% and 2.5% respectively in the group receiving HDRPB and 3.1% and 8.2% respectively in the group receiving EBRT alone (p<0.01) (Wedde et al, 2018).
- **Biochemical relapse-free survival** (RFS). (One study, n=216). RFS (including measures of PSA and clinical relapse) at 5, 7 and 10 years respectively was 75%, 66% and 46% in the group receiving HDRPB and 61%, 48% and 39% in those receiving EBRT alone (p=0.04) (Hoskin et al, 2012).
- **Freedom from biochemical failure** (FFBF). (One study, n=688). FFBF (assessed by PSA) at 5 and 10 years respectively was 79.8% and 69.2% in the group receiving HDRPB and 70.9% and 32.8% in the group receiving EBRT alone (p=0.0011) (Khor et al, 2013).

- **Freedom from metastases** (FFM). (One study, n=688). FFM (not defined) at 5 years was 90.0% in the group receiving HDRPB and 91.0% in the group receiving EBRT alone (p=0.27) (Khor et al, 2013).

**High dose rate brachytherapy boost with EBRT versus radical prostatectomy**

- **Overall mortality** (OM). (One study, n=89). Lennernas et al (2015) reported that at least 10 years after randomisation there had been 2 deaths due to prostate cancer and 7 due other causes in the group treated with HDRPB (n=44), and 6 due to prostate cancer and 6 due to other causes in those treated with RP (n=45). The significance of differences between groups was not reported.
- **Biochemical failure-free control rate** (BFFCR). (One study, n=150). BFFCR (assessed by PSA) at 3 years and 5 years respectively was 92% and 85% for patients receiving HDRPB and 72% and 72% for those undergoing RP (p<0.0012). This was the result for the whole cohort which included an unspecified number of low risk patients[4]. BFFCR for intermediate risk patients only at 3 and 5 years respectively was 92% and 92% for patients receiving HDRPB and 73% and 73% for those receiving RP (p<0.0492). BFFCR for high risk patients only at 3 and 5 years respectively was 94% and 72% for patients receiving HDRPB and 45% and 45% for those receiving RP (p<0.0073) (Noda et al, 2011).

**High dose rate brachytherapy boost with EBRT versus EBRT alone versus radical prostatectomy**

- **Overall survival** (OS). (One study, n=487). OS at 5 and 10 years respectively was 84.7% and 59.2% in the group receiving HDRPB, 79.9% and 65.3% in the group receiving EBRT alone, and 90.3% and 72.1% in the group receiving RP. There was no statistically significant difference in OS between the group receiving HDRPB and either of the other two treatment groups (HDRPB vs EBRT: HR=0.99 (95%CI 0.58-1.98), p=0.98; HDRPB vs RP: HR=1.06 (95%CI 0.53-2.12), p=0.8688).
- **Prostate cancer-specific mortality** (PCSM). (One study, n=487). PCSM at 5 and 10 years respectively was 4.4% and 11.9% in the group receiving HDRPB, 8.4% and 19.5% in the group receiving EBRT alone, and 8.3% and 21.5% in the group receiving RP. There was no statistically significant difference in PCSM between the group receiving HDRPB and either of the other two treatment groups (HDRPB vs EBRT: HR=0.64 (95%CI 0.24-1.71), p=0.37; HDRPB vs RP: HR=0.48 (95%CI 0.16-1.4), p=0.18).
- **Biochemical recurrence** (One study, n=487). Biochemical recurrence at 5 and 10 years respectively was 17.1% and 30.0% in the group receiving HDRPB, 28.2% and 39.7% in the group receiving EBRT alone, and 73.6% and 83.8% in the group receiving RP. There was no statistically significant difference in biochemical recurrence between the group receiving HDRPB and those receiving EBRT (HR=0.76 (95%CI 0.44-1.32), p=0.33). The rate of biochemical recurrence was statistically significantly lower in the group receiving HDRPB than the group receiving RP (HR=0.16 (95%CI 0.09-0.28), p<0.0001)[5].
- **Distant metastases** (DM). (One study, n=487). The rate of DM at 5 and 10 years respectively was 5.4% and 10.2% in the group receiving HDRPB, 20.9% and 33.3% in

[4] Risk categories did not correspond to those defined by NCCN or NICE

[5] Biochemical recurrence was defined for RP patients as a postoperative PSA of ≥0.2ng/ml or initiation of salvage therapy, and for HDRPB and EBRT patients as a PSA ≥2ng/ml above the nadir for that patient or the initiation of salvage therapy

the group receiving EBRT alone, and 20.9% and 38.5% in the group receiving RP. The rate of DM was statistically significantly lower in the group receiving HDRPB than in both the group receiving EBRT (HR=0.30 (95%CI 0.12-0.72), p=0.008) and the group receiving RP (HR=0.23 (95%CI 0.09-0.6), p=0.003)[6].

**Safety**

**High dose rate brachytherapy boost with EBRT versus EBRT alone**

- **Genitourinary (GU) adverse events** (One study, n=216). The cumulative incidence of GU adverse events[7] by 5 and 7 years respectively was 26% and 31% in the group receiving HDRPB and 26% and 30% in those receiving EBRT alone (p=0.5). The prevalence of GU adverse events at 5 and 7 years respectively was 8% and 11% in the group receiving HDRPB and 9% and 4% in those receiving EBRT alone (p=1.0 (5 years), p=0.4 (7 years)) (Hoskin et al, 2012).
- **Gastrointestinal (GI) adverse events** (One study, n=216). The cumulative incidence of GI adverse events[8] by 5 and 7 years respectively was 7% and 7% in the group receiving HDRPB and 6% and 6% in those receiving EBRT alone (p=0.8). The prevalence of GI adverse events at 5 and 7 years respectively was 0% and 0% in the group receiving HDRPB and 0% and 2% in those receiving EBRT alone (p=1.0) (Hoskin et al, 2012).
- **Urethral stricture** (Two studies, n=216 and n=688). The cumulative incidence of urethral stricture requiring surgical management by 5 and 7 years respectively was 6% and 8% in the group receiving HDRPB and 2% and 2% in those receiving EBRT alone (p=0.1) (Hoskin et al, 2012). Khor et al reported a 5-year cumulative incidence of Grade 3 stricture (requiring operative intervention) of 11.8% (95%CI 8.1%-16.5%) in the group receiving HDRPB and 0.3% (95%CI 0%-0.9%) in those receiving EBRT alone (p<0.0001). They also reported a 5-year combined cumulative incidence of Grade 2 (requiring catheterisation or dilatation) or Grade 3 strictures of 16.8% (95%CI 12.6%-22.1%) in the group receiving HDRPB and 1.9% (95%CI 0.6%-3.6%) in those receiving EBRT alone (p<0.0001).

**High dose rate brachytherapy boost with EBRT versus radical prostatectomy**

- **Health-related quality of life (HRQoL)**. (One study, n=89). Lennernas et al (2015) reported scores for a number of HRQoL scales[9] at randomisation and at 12 and 24 months. They found no significant difference between groups treated with HDRPB or RP in scores for physical, role, emotional, cognitive or social functioning or in global QoL (p values not reported). They found an overall significant improvement over time in emotional functioning (p=0.0005) and an overall significant deterioration over time in social functioning (p=0.0051) for the whole study population. They found no significant differences between groups treated with HDRPB or RP or over time in symptoms of fatigue, pain, insomnia, constipation or diarrhoea (p values not reported).

[6] DM were classified as imaging evidence of lesions that were clinically or pathologically diagnosed as metastatic

[7] Defined as: urinary diversion; frequency at night ≥6x; intermittent or persistent incontinence; intermittent or daily haematuria, blood clots; score 3 for urgency or dysuria.

[8] Defined as: frequency ≥6x /day; faecal consistency liquid; blood loss intermittent or daily, gross haemorrhage; rectal discharge intermittent or persistent requiring surgical treatment.

[9] Measured using the European Organization of Research and Treatment of Cancer Quality of Life Questionnaire C33 (EORTC QLQ-C33). This comprises 33 items incorporating five single-item scales and nine multi-item scales evaluating function (physical, role, cognitive, emotional, and social), symptoms (fatigue, pain, nausea/vomiting, sleeping problems, constipation, appetite loss, dyspnoea, diarrhoea), and global health and QoL.

- **Urinary and sexual function.** (One study, n=89). Lennernas et al (2015) reported scores for urinary, bowel and sexual function using a prostate cancer-specific questionnaire[10] at randomisation and at 12 and 24 months. They reported no statistically significant differences between groups treated with HDRPB or RP (p values not reported). They reported an overall significant deterioration over time in scores of urinary incontinence and erectile problems (urinary incontinence p=0.0011; erectile problems p<0.0001).

**Cost and cost-effectiveness**

**High dose rate brachytherapy boost with EBRT versus EBRT alone**

- **Expected lifetime treatment costs** (One study). The estimated lifetime cost of treatment for the base case estimates reported by Vu et al (2018) were US$68,696 for patients receiving HDRPB and US$114,944 for patients receiving IMRT alone. For alternative case 1 (assuming worse outcomes, higher toxicity and greater costs for brachytherapy than the base case) the estimated lifetime costs were US$106,143 for HDRPB and US$102.238 for IMRT alone. For alternative case 2 (assuming better outcomes, lower toxicity and lower costs for brachytherapy than the base case) the estimated lifetime costs were US$42,817 for HDRPB and US$111,738 for IMRT alone. The statistical significance of differences was not reported and cost-effectiveness for the base case was not reported.
- **Expected quality adjusted life years** (QALYs). (One study). The estimated QALYs for the base case estimates reported by Vu et al (2018) were 10.8 years for patients receiving HDRPB and 9.3 years for patients receiving IMRT alone. For alternative case 1 (assuming worse outcomes, higher toxicity and greater costs for brachytherapy than the base case) the estimated QALYs were 9.49 years for HDRPB and 9.3 years for IMRT alone. For alternative case 2 (assuming better outcomes, lower toxicity and lower costs for brachytherapy than the base case) the estimated QALYs were 12.07 years for HDRPB and 9.3 years for IMRT alone. The statistical significance of differences was not reported and cost-effectiveness for the base case was not reported.

There were some limitations to all the studies included in this RER. The RCT reported by Hoskin et al (2012) appears to have been a well-conducted RCT whose findings should be reliable, but EBRT was delivered to a lower dose (55 Gy) than the current NICE recommendation (at least 74 Gy). The second RCT, Lennernas et al (2015) closed early after recruiting only about a quarter of the subjects planned, and is significantly underpowered to detect differences in any of the outcomes reported. The four retrospective studies each compared a cohort treated with HRDPB with one treated with either EBRT (Wedde et al, 2018, and Khor et al, 2013) or RP (Noda et al, 2011), or two cohorts treated with either EBRT or RP (Kishan et al, 2017). All have a risk of bias associated with their methodology; of the four, the cohorts compared in Khor et al (2013) appear to have been more closely matched than those in the other three studies. The cost-effectiveness study uses US costs which are not generalisable to the UK, and appears to have major flaws associated with the assumptions used in their model, which reduces the reliability of their findings (Vu et al, 2018).

[10] A prostate cancer-specific HRQoL questionnaire consisting of 20 items which was developed in Gothenburg, Sweden, to gather information on specific problems experienced with respect to bowel, urinary tract, and sexual functions.

## 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: PubMed, Embase and Cochrane Library (see section 10 for search strategy).
- The search dates for publications were between 1 January 2008 and 22 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. Papers which matched the PICO were selected for inclusion in this review, prioritising RCTs and better designed comparative studies.
- Evidence from all papers included 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 below).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8 below).

## 4 Results

This rapid evidence review identified seven studies for inclusion. Six studies compared the clinical effectiveness of external beam radiotherapy plus high dose rate brachytherapy boost (HDRPB) with other in-scope treatment approaches for intermediate and high risk localised prostate cancer. In three studies the comparator was external beam radiotherapy (EBRT); one reported a RCT (Hoskin et al, 2012), and two were retrospective analyses of two treatment cohorts (Wedde et al, 2018; Khor et al, 2013). In two studies the comparator was radical prostatectomy (RP); one (Lennernas et al, 2015) was a small RCT, and the other was a retrospective analysis of two treatment cohorts (Noda et al, 2011). One study was a retrospective analysis which included both EBRT and RP as comparators (Kishan et al, 2017).

One study (Vu et al, 2018) compared the cost-effectiveness of HDRPB with EBRT.

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 high dose rate brachytherapy boost to external beam radiotherapy compared to external beam therapy alone or surgery?**

Clinical outcomes reported included overall survival, overall mortality, prostate cancer-specific mortality, biochemical relapse-free survival, freedom from biochemical failure, biochemical failure-free control rate, biochemical recurrence, freedom from metastases and distant metastases.

**High dose rate brachytherapy boost with EBRT versus EBRT alone**

**Overall survival**
One study reported overall survival (OS). Hoskin et al (2012) reported OS at 5, 7 and 10 years respectively of 88%, 81% and 67% in the group receiving HDRPB and 89%, 88% and 79% in those receiving EBRT alone. There was no statistically significant difference between the groups (p=0.2).

**Overall mortality**
One study reported overall mortality (OM). Wedde et al (2018) reported that OM at 10 years was 12.92% (42/325) in the group receiving HDRPB and 23.31% (69/296) in the group receiving EBRT alone (p=0.02).

**Prostate cancer-specific mortality**
One study reported prostate cancer-specific mortality (PCSM). Wedde et al (2018) reported that PCSM at 5 and 10 years was 1% and 2.5% (7/325) respectively in the group receiving HDRPB and 3.1% and 8.2% (25/296) respectively in the group receiving EBRT alone (p<0.01).

**Biochemical relapse-free survival**
One study reported biochemical relapse-free survival (RFS). Hoskin et al (2012) used a broad definition of biochemical and clinical relapse, and reported RFS at 5, 7 and 10 years respectively of 75%, 66% and 46% in the group receiving HDRPB and 61%, 48% and 39% in those receiving EBRT alone (p=0.04).

**Freedom from biochemical failure**
One study reported freedom from biochemical failure (FFBF)[11]. Khor et al (2013) reported FFBF at 5 and 10 years respectively of 79.8% and 69.2% in the group receiving HDRPB and 70.9% and 32.8% in the group receiving EBRT alone (p=0.0011).

**Freedom from metastases**
One study reported freedom from metastases (FFM) (not defined). Khor et al (2011) reported FFM at 5 years of 90.0% in the group receiving HDRPB and 91.0% in the group receiving EBRT alone (p=0.27).

**High dose rate brachytherapy boost with EBRT versus radical prostatectomy**

**Overall mortality**
One study reported overall mortality (OM). Lennernas et al (2015) reported that at least 10 years after randomisation there had been 2 deaths due to prostate cancer in the group treated with HDRPB (n=44) and 6 in those treated with RP (n=45). At the same point there had been 7 deaths due to other causes in the group treated with HDRPB and 6 in those treated with RP. The significance of differences between groups was not reported.

**Biochemical failure-free control rate**
One study reported biochemical failure-free control rate (BFFCR)[12]. Noda et al (2011) reported a BFFCR at 3 years and 5 years respectively of 92% and 85% for patients receiving HDRPB and 72% and 72% for those undergoing RP (p<0.0012). This was the result for their whole cohort

[11] Biochemical failure defined as an increase of ≥2ng/ml above PSA nadir
[12] Biochemical failure defined as an increase of ≥2ng/ml above PSA nadir

which included an unspecified number of low risk patients[13]. They reported a BFFCR for intermediate risk patients only at 3 years and 5 years respectively of 92% and 92% for patients receiving HDRPB and 73% and 73% for those receiving RP (p<0.0492). They also reported a BFFCR for high risk patients only at 3 years and 5 years respectively of 94% and 72% for patients receiving HDRPB and 45% and 45% for those receiving RP (p<0.0073).

**High dose rate brachytherapy boost with EBRT versus EBRT alone versus radical prostatectomy**

**Overall survival**
One study reported overall survival (OS). Kishan et al (2017) reported estimated OS at 5 and 10 years respectively of 84.7% and 59.2% in the group receiving high dose rate brachytherapy boost with EBRT (HDRPB), 79.9% and 65.3% in the group receiving EBRT alone, and 90.3% and 72.1% in the group receiving RP. There was no statistically significant difference in OS between the group receiving HDRPB and either of the other two treatment groups (HDRPB vs EBRT: HR=0.99 (95%CI 0.58-1.98), p=0.98; HDRPB vs RP: HR=1.06 (95%CI 0.53-2.12), p=0.8688).

**Prostate cancer-specific mortality**
One study reported prostate cancer-specific mortality (PCSM). Kishan et al (2017) reported estimated PCSM at 5 and 10 years respectively of 4.4% and 11.9% in the group receiving HDRPB, 8.4% and 19.5% in the group receiving EBRT alone, and 8.3% and 21.5% in the group receiving RP. There was no statistically significant difference in PCSM between the group receiving HDRPB and either of the other two treatment groups (HDRPB vs EBRT: HR=0.64 (95%CI 0.24-1.71), p=0.37; HDRPB vs RP: HR=0.48 (95%CI 0.16-1.4), p=0.18).

**Biochemical recurrence**
One study reported biochemical recurrence. Kishan et al (2017) reported biochemical recurrence at 5 and 10 years respectively of 17.1% and 30.0% in the group receiving HDRPB, 28.2% and 39.7% in the group receiving EBRT alone, and 73.6% and 83.8% in the group receiving RP. There was no statistically significant difference in biochemical recurrence between the group receiving HDRPB and those receiving EBRT (HR=0.76 (95%CI 0.44-1.32), p=0.33). The rate of biochemical recurrence was statistically significantly lower in the group receiving HDRPB than the group receiving RP (HR=0.16 (95%CI 0.09-0.28), p<0.0001)[14].

**Distant metastases**
One study reported distant metastases (DM). Kishan et al (2017) reported a rate of DM at 5 and 10 years respectively of 5.4% and 10.2% in the group receiving HDRPB, 20.9% and 33.3% in the group receiving EBRT alone, and 20.9% and 38.5% in the group receiving RP. The rate of DM was statistically significantly lower in the group receiving HDRPB than in both the group receiving EBRT (HR=0.30 (95%CI 0.12-0.72), p=0.008) and the group receiving RP (HR=0.23 (95%CI 0.09-0.6), p=0.003)[15].

[13] Risk categories did not correspond to those defined by NCCN or NICE
[14] Biochemical recurrence was defined for RP patients as a postoperative PSA of ≥0.2ng/ml or initiation of salvage therapy, and for HDRPB and EBRT patients as a PSA ≥2ng/ml above the nadir for that patient or the initiation of salvage therapy
[15] DM were classified as imaging evidence of lesions that were clinically or pathologically diagnosed as metastatic

**2. What is the safety of adding a high 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 outcomes reported included genitourinary adverse events, gastrointestinal adverse events, urethral stricture, health-related quality of life, urinary and sexual function.

**High dose rate brachytherapy boost with EBRT versus EBRT alone**

**Genitourinary adverse events**

One study reported genitourinary (GU) adverse events[16]. Hoskin et al (2012) reported a cumulative incidence of GU adverse events by 5 and 7 years respectively of 26% and 31% in the group receiving HDRPB and 26% and 30% in those receiving EBRT alone. The difference between the groups was not statistically significant (p=0.5). They also reported the prevalence of GU adverse events at 5 and 7 years respectively of 8% and 11% in the group receiving HDRPB and 9% and 4% in those receiving EBRT alone. The differences were not statistically significant (p=1.0 (5 years), p=0.4 (7 years)).

**Gastrointestinal adverse events**

One study reported gastrointestinal (GI) adverse events[17]. Hoskin et al (2012) reported a cumulative incidence of GI adverse events by 5 and 7 years respectively of 7% and 7% in the group receiving HDRPB and 6% and 6% in those receiving EBRT alone. The difference between the groups was not statistically significant (p=0.8). They also reported the prevalence of GI adverse events at 5 and 7 years respectively of 0% and 0% in the group receiving HDRPB and 0% and 2% in those receiving EBRT alone (p=1.0).

**Urethral stricture**

Two studies reported urethral stricture. Hoskin et al (2012) reported a cumulative incidence of urethral stricture requiring surgical management by 5 and 7 years respectively of 6% and 8% in the group receiving HDRPB and 2% and 2% in those receiving EBRT alone (p=0.1). Khor et al (2013) reported a 5-year cumulative incidence of Grade 3 stricture (requiring operative intervention) of 11.8% (95%CI 8.1%-16.5%) in the group receiving HDRPB and 0.3% (95%CI 0%-0.9%) in those receiving EBRT alone (p<0.0001). They also reported a 5-year combined cumulative incidence of Grade 2 (requiring catheterisation or dilatation) or Grade 3 strictures of 16.8% (95%CI 12.6%-22.1%) in the group receiving HDRPB and 1.9% (95%CI 0.6%-3.6%) in those receiving EBRT alone (p<0.0001).

**High dose rate brachytherapy boost with EBRT versus radical prostatectomy**

**Health-related quality of life**

[16] Defined as: urinary diversion; frequency at night ≥6x; intermittent or persistent incontinence; intermittent or daily haematuria, blood clots; score 3 for urgency or dysuria.

[17] Defined as frequency ≥6x /day; faecal consistency liquid; blood loss intermittent or daily, gross haemorrhage; rectal discharge intermittent or persistent requiring surgical treatment.

One study reported health-related quality of life (HRQoL)[18]. Lennernas et al (2015) reported scores for a number of the scales of the EORTC QLQ-C33 at randomisation and at 12 and 24 months. They found no significant difference between groups treated with HDRPB or RP in scores for physical, role, emotional, cognitive or social functioning or in global QoL (p values not reported). They found an overall significant improvement over time in emotional functioning (p=0.0005) and an overall significant deterioration over time in social functioning (p=0.0051) for the whole study population. They found no significant difference between groups treated with HDRPB or RP or over time in scores for symptoms of fatigue, pain, insomnia, constipation or diarrhoea (p values not reported).

**Urinary and sexual function**
One study assessed urinary, bowel and sexual function using a prostate cancer-specific HRQoL questionnaire[19] at randomisation and at 12 and 24 months. Lennernas et al (2015) reported no statistically significant differences between groups treated with HDRPB or RP (not all items were reported; p values not reported). They reported an overall significant deterioration over time in scores of urinary incontinence and erectile problems (urinary incontinence p=0.0011; erectile problems p<0.0001).

**3. What is the cost effectiveness of adding a high 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?**

Cost and cost-effectiveness outcomes reported included expected lifetime treatment costs and expected QALYs.

**High dose rate brachytherapy boost with EBRT versus EBRT alone**

**Expected lifetime treatment costs**
One study reported expected lifetime treatment costs. Vu et al (2018) reported the estimated lifetime cost of treatment for their base case estimates to be $68,696 for patients receiving HDRPB and $114,944 for patients receiving IMRT alone. For alternative case 1 (assuming worse outcomes, higher toxicity and greater costs for brachytherapy than the base case) their estimated lifetime costs were $106,143 for HDRPB and $102.238 for IMRT alone. For alternative case 2 (assuming better outcomes, lower toxicity and lower costs for brachytherapy than the base case) their estimated lifetime costs were $42,817 for HDRPB and $111,738 for IMRT alone. The statistical significance of differences was not reported and cost-effectiveness for the base case was not reported.

**Expected quality adjusted life years**
One study reported expected quality adjusted life years (QALYs). Vu et al (2018) reported the estimated QALYs for their base case estimates to be 10.8 years for patients receiving HDRPB and 9.3 years for patients receiving IMRT alone. For alternative case 1 (assuming worse outcomes, higher toxicity and greater costs for brachytherapy than the base case) their estimated QALYs were 9.49 years for HDRPB and 9.3 years for IMRT alone. For alternative case 2

[18] Measured using the European Organization of Research and Treatment of Cancer Quality of Life Questionnaire C33 (EORTC QLQ-C33). This comprises 33 items incorporating five single-item scales and nine multi-item scales evaluating function (physical, role, cognitive, emotional, and social), symptoms (fatigue, pain, nausea/vomiting, sleeping problems, constipation, appetite loss, dyspnoea, diarrhoea), and global health and QoL.
[19] A prostate cancer-specific HRQoL questionnaire consisting of 20 items which was developed in Gothenburg, Sweden, to gather information on specific problems experienced with respect to bowel, urinary tract, and sexual functions.

(assuming better outcomes, lower toxicity and lower costs for brachytherapy than the base case) their estimated QALYs were 12.07 years for HDRPB and 9.3 years for IMRT alone. The statistical significance of differences was not reported.

## 5 Discussion

This review included three studies comparing the clinical effectiveness of external beam radiotherapy pus high dose rate brachytherapy boost (HDRPB) with external beam radiotherapy alone (EBRT) in intermediate or high risk prostate cancer. One was a RCT including 216 subjects (Hoskin et al, 2012), which appears to have been well-conducted but which delivered EBRT to a lower dose than the current NICE (NICE 2014b) or NHS England (NHS England 2017) recommendations. Its relevance to current practice is therefore limited. Two studies were retrospective analyses of two treatment cohorts including 621 and 688 subjects respectively (Wedde et al, 2018; Khor et al, 2013); while these are subject to the biases inherent in this type of study, the cohorts in Khor et al (2013) appear to have been more closely matched. The use of androgen deprivation therapy (ADT) varied between studies; NICE currently recommends that it should be offered to all men undergoing radical radiotherapy, but it was received by only 76% of men in Hoskin et al (2012) and 59% of those in Khor et al (2013). All those in Wedde et al (2018) received ADT, but for a different duration in the two treatment groups.

In two further studies included in this review the comparator was radical prostatectomy (RP). Lennernas et al (2015) was a small RCT which appears to have been well-designed but which was significantly underpowered because recruitment closed early with only 89 subjects. Noda et al (2011) was a retrospective analysis of two treatment cohorts with a total of 150 subjects and a number of sources of bias. The risk group (using the NCCN definition) of patients in these two studies was not reported; while it appears the majority were probably intermediate or high risk, Noda et al (2011) included an unspecified number of patients who met criteria for low risk. All patients in Lennernas et al (2015) received 6 months' ADT, but no patients in Noda et al (2011) received ADT. One further included study was a retrospective analysis including 487 high risk subjects with two comparator groups who received either EBRT or RP (Kishan et al, 2017). Again, there were a number of sources of bias including differences between the groups in baseline characteristics, approaches to treatment and measurement of outcomes.

There was limited information on the effect on mortality of HDRPB compared with other treatment approaches. The RCT reported by Hoskin et al (2012) found no significant benefit over EBRT in overall mortality at up to 10 years follow-up, but their study was not powered to detect mortality differences. Kishan et al (2017) did not find any benefit in overall survival or prostate cancer-specific mortality up to 10 years after treatment for patients treated with HDRPB compared with either EBRT or RP. Wedde et al (2018) reported significant improvements in both overall mortality and prostate cancer-specific mortality at 10 years for the HDRPB group compared with EBRT, but this study had significant biases which reduce the reliability of these findings.

The evidence on the effect of HDRPB compared with other approaches on measures of disease progression was more convincing. Hoskin et al (2012) found a significant improvement in relapse-free survival (including measures of biochemical and clinical relapse) which was around one-third higher in the HDRPB group than the EBRT group at 7 years, but the difference had narrowed to about one-seventh higher by 10 years. Significant reductions in biochemical failure (based on PSA levels alone) were also reported in two of the retrospective studies, one of which also compared HDRPB with EBRT (Khor et al, 2013), and the other of which compared HDRPB with

RP (Noda et al, 2011). Khor et al (2013) found that around 90% of all subjects were free from metastases at 5 years, with no difference between those treated with HDRPB and EBRT. In contrast, Kishan et al (2017) found significantly lower rates of distant metastases in patients treated with HDRPB than those treated with either EBRT or RP. Both these were retrospective studies with a number of sources of bias and it is not possible to say which finding should be viewed as more reliable.

The risk of genitourinary (GU) adverse events is a major concern associated with radiotherapy treatment for prostate cancer. GU adverse events were reported to have occurred in almost a third of all patients in the Hoskin et al (2012) RCT up to 7 years after treatment, but there was no significant difference between treatment groups. While they reported higher rates of urethral stricture requiring surgical intervention in the HDRPB group than the EBRT group, overall numbers reported were low and the difference between groups was not statistically significant. In contrast, Khor et al (2013) found an over thirty-fold higher incidence of urethral stricture in HDRPB patients compared with EBRT. This study identified urethral stricture retrospectively according to whether patients had needed operative intervention, so there is a risk of bias associated with this finding. Gastrointestinal adverse events were much less common, occurring in only 6-7% of all patients in Hoskin et al (2012), with no difference between treatment groups.

In comparing HDRPB with surgery, the small RCT reporting changes in health-related quality of life (HRQoL) up to 2 years after treatment found that the whole study population reported a significant deterioration in social functioning and in urinary incontinence and erectile problems, but a significant improvement in emotional functioning (Lennernas et al, 2015). However there were no significant differences between HDRPB and RP treatment groups in any HRQoL measures.

This review included one cost-effectiveness study of HDRBP versus IMRT in patients with localised prostate cancer at intermediate and high risk (Vu et al, 2018). This study used US costs and estimated that the lifetime treatment cost of their base case was over 50% higher for patients receiving IMRT alone compared with HDRPB, with fewer expected QALYs for the IMRT group, but these relative differences changed significantly with changes in their assumptions. The model appears to have used questionable assumptions so the findings must be regarded as unreliable. No studies reported findings on the cost-effectiveness of HDRPB compared with treatment approaches other than EBRT.

Overall, the findings of the studies included in this review suggest that treatment of intermediate or high risk localised prostate cancer with HDRPB may reduce disease progression compared with treatment with EBRT, but it was unclear whether this translated into improved survival. GU adverse events were experienced by a significant proportion of subjects in all the studies which reported them, but evidence was mixed on whether HDRPB increased the risk of GU adverse events compared with EBRT or RP. While delivering HDRPB appeared to cost more than IMRT or LDRBT alone, there was no reliable evidence on how this related to overall treatment costs or outcomes.

These 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 HDRPB compared with EBRT or RP.

To provide more conclusive evidence of the benefits and risks associated with HDRPB compared with other treatments, larger randomised studies would be required which include currently recommended treatment regimes and are 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.

## 6 Conclusion

The best evidence on the clinical effectiveness of HDRPB compared with other treatment approaches for intermediate or high risk localised prostate cancer comes from the RCT reported by Hoskin et al (2012), which included 216 subjects and found a significant improvement in relapse-free survival (including measures of biochemical and clinical relapse) in the HDRPB group compared with EBRT alone. It was unclear whether this translated into improved survival, which this study was not powered to detect, and there was mixed evidence on whether HDRPB was associated with an increased risk of GU adverse events compared with other treatment approaches.

Reducing the risk of relapse of prostate cancer is an important outcome for patients, their families and clinicians, as it is likely to be associated with increased morbidity and mortality, although the studies included in this review did not provide conclusive evidence of this. They also provide limited evidence on the likely balance between benefits and risks for patients undergoing HDRPB or other treatments. This information would be extremely important for patients and their clinicians making a decision about treatment. Further well-designed studies are needed to provide evidence on the clinical effectiveness, cost-effectiveness and safety of HDRPB and other treatment options for intermediate or high risk localised prostate cancer

## 7 Evidence Summary Table

For abbreviations see list after tables

| a) Use of High dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| Wedde et al 2018 | P1<br><br>Retrospective analysis comparing 2 cohorts.<br><br>Multiple treatment centres, Norway | n=621<br><br>High risk (met at least one of the NCCN criteria for high risk)<br><br>Median age 66yrs<br><br>n=325 HDR-EBRT<br><br>n=296 EBRT<br><br>Significant difference (p<0.001) between groups (HDR-EBRT vs EBRT) in:<br><br>GS:<br>GS6: 8%vs17%<br>GS7: 54%vs66%<br>GS8-10: 38%vs17%<br><br>T stage:<br>T1: 8%vs0 | HDR-EBRT: EBRT to 50Gy, HDRBT using Iridium 192, 2 yrs ADT<br><br>EBRT: 3D conformal EBRT of 50 Gy in 25 fractions to prostate and seminal vesicles; boost of 20 Gy in 10 fractions to prostate gland. Lifelong antiandrogen treatment.<br><br>Cases treated between 2004-09, controls between 1996-2002. Reasons for treatment allocation were not described. Different methods were used for | Primary<br><br>Clinical effectiveness | Overall mortality (OM) at 10 yrs, %<br><br>Hazard ratio (HR) | HDR-EBRT<br>Total deaths n=42 (12.92%)<br><br>EBRT<br>Total deaths n=69 (23.31%)<br><br>HR 1.63 (95%CI 1.08–2.44) p=0.02 | 4 | Direct | This study retrospectively analysed and compared 2 different cohorts treated for high risk prostate cancer (NCCN definition).<br><br>Median follow-up was 104 and 120 months for the HDR-EBRT and the EBRT group respectively. Cause of death was obtained from the Norwegian National Registry. Outcomes were timed from the start of hormone treatment.<br><br>There were significant differences at baseline in GS and T stage, with more of the HDR-EBRT group having higher GS, and more of the EBRT group having higher T stage.<br><br>There were also differences in approach to assessment/ tumour staging, in treatment setting (the HDR-EBRT group were treated in one tertiary centre, while the EBRT group were treated in multiple settings), in time period of treatment, and hormone treatment given. All patients were reported to have had ADT, which is in line with NICE's recommendation that radiotherapy and ADT should be offered together; however HDR-EBRT patients received it for 2 yrs whereas for the EBRT patients it was 'lifelong'. EBRT was given to a total of 70Gy in 2Gy fractions which is close to the current NICE recommended minimum of 74Gy (NICE 2014b).<br><br>The authors reported that patients treated with HDR-EBRT had significantly lower OM and PCSM at 10 yrs.<br><br>These findings must be viewed as only moderately reliable due to the sources of potential bias; the retrospective analysis, unmatched cohorts, |
| | | | | Primary<br><br>Clinical effectiveness | Prostate cancer-specific mortality (PCSM) at 5 and 10 yrs, % (95%CI)<br><br>Hazard ratio (HR) | HDR-EBRT<br>5-year: 1% (0.3–2.2)<br>10-year: 2.5% (1.0–5.5)<br>Total prostate cancer deaths: n=7 (2.15%)<br><br>EBRT<br>5year: 3.1% (2.5–5.8)<br>10-year 8.2% (5.5–12.0)<br>Total prostate cancer deaths: n=25 (8.45%)<br><br>HR 3.58 (95%CI 1.40–9.14) p<0.01 | | | |

| a) Use of High dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| | | T2: 21%vs10%<br>T3: 71%vs90%<br><br>No significant difference in PSA:<br>0-10: 21%vs30%<br>11-19.9: 30.5%vs28%<br>≥20: 48.5%vs42% | tumour assessment over time and in the 2 groups | | | | | | differences between the groups identified above and other likely confounders. |
| Vu et al 2018 | S2<br><br>Cost-effectiveness modelling study<br><br>Uses USA costs | Patients with intermediate-high risk prostate cancer | Two treatment options were modelled:<br><br>HDRPB: 23 fractions of IMRT and two fractions of HDR prostate brachytherapy<br><br>IMRT: 44 fractions of IMRT alone<br><br>All patients received 1 year of ADT<br><br>The model assumed further treatment with | Secondary<br><br>Cost | Expected lifetime cost | Base case<br>HDRPB: US$68,696<br>IMRT: US$114,944<br><br>Alternative 1<br>HDRPB: US$106,143<br>IMRT: US$102.238<br><br>Alternative 2<br>HDRPB: US$42,817<br>IMRT: US$111,738 | 3 | Direct | This study used a Markov model to estimate cost-effectiveness of HDRPB compared with IMRT.<br><br>Various sources are used for model assumptions. Transition probability between the localized and recurrent cancer state for the different treatment approaches was estimated from the 9-year biochemical progression-free survival (bPFS) reported in the ASCENDE-RT trial (Morris et al 2017). However this trial compared LDRPB with DE-EBRT to 78Gy, not HDRPB with IMRT. The model assumed all patients received ADT which is in line with NICE's recommendation that radiotherapy and ADT should be offered together;<br>Risk of progression from recurrent cancer state to hormone-resistant metastatic prostate cancer state, and from that state to death, was estimated from other published studies.<br>Outcomes and toxicity data for the HDRPB and IMRT treatment approaches were also based on ASCENDE-RT.<br>The ASCENDE-RT findings were said to be 'concordant with' the authors' own outcomes for |
| | | | | Secondary<br><br>Cost-effectiveness | Expected QALYs (reported in yrs) | Base case<br>HDRPB: 10.8yrs<br>IMRT: 9.3yrs<br><br>Alternative 1<br>HDRPB: 9.49yrs<br>IMRT: 9.30yrs<br><br>Alternative 2<br>HDRPB: 12.07yrs<br>IMRT: 9.30yrs | | | |

| a) Use of High dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Study reference | Study Design | Population characteristics | Intervention | Outcome measure type | Outcome measures | Results | Quality of Evidence Score | Applicability | Critical Appraisal Summary |
| | | | ADT and with systemic therapy for subjects whose cancer progressed | | | | | | patients receiving HDRPB vs IMRT as well as with the Hoskin et al (2012) trial of HDRPB vs EBRT. However the authors' reference to their results appears to be a conference presentation, no abstract is available. Published results for bPFS from the other two cited studies are summarised below and suggest the findings are not 'concordant':<br><br>ASCENDE (Morris et al 2017) (bPFS, %+/- SD)<br>DE-EBRT<br>5y: 83.8% +/- 5.6<br>7y: 75.0% +/- 7.2<br>9y: 62.4% +/- 9.8<br><br>LDRPB<br>5y: 88.7% +/- 4.8<br>7y: 86.2% +/- 5.4<br>9y: 83.3% +/- 6.6<br><br>Hoskin et al (2012) (bPFS, %)<br>EBRT:<br>5y: 61% 7y: 48%<br>HDRPB<br>5y: 75% 7y: 66%<br><br>The authors do not clarify how the assumptions used in the model were derived from the ASCENDE-RT results.<br>A published source was used for the estimated utilities of various prostate cancer states.<br>Costs were US costs, using Medicare reimbursement and other sources, so may not reflect actual treatment costs.<br><br>QALYs and expected lifetime costs of the two treatment approaches were presented for base case and two alternative sets of assumptions, which were:<br>Alternative 1: assumed worse outcomes, higher toxicity and greater costs for brachytherapy than the base case. |

| a) Use of High dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| | | | | | | | | | Alternative 2: assumed better outcomes, lower toxicity and lower costs for brachytherapy than the base case.<br><br>The authors concluded that IMRT with HDRBT boost is a cost-effective treatment for intermediate-high risk prostate cancer compared to IMRT alone.<br>However the findings cannot be regarded as reliable because:<br>The costs are based on a treatment regime using HDRPB and IMRT but assumptions about outcomes are based on ASCENDE-RT which used LDRPB and DE-EBRT. No published evidence could be found suggesting that the results of these different treatment approaches were sufficiently similar to justify using them interchangeably in a cost-effectiveness model.<br>It was not clear how the assumptions had been derived from ASCENDE-RT.<br>Findings are reported only as 'expected QALYs' and 'lifetime costs' of each treatment approach.<br>The US costs used are not generalisable to the UK. |
| Khor et al 2013 | P1<br><br>Retrospective analysis of matched cohorts<br><br>Single centre, Australia | n=688<br>41% high risk; 59% intermediate risk (NCCN)<br><br>n=344 HDRPB<br>n=344 EBRT<br><br>Treatment allocation | HDRPB: EBRT 46 Gy in 23 fractions with HDRB boost of 19.5 Gy in 3 fractions<br><br>EBRT: EBRT 74 Gy in 37 fractions | Primary<br><br>Clinical effectiveness | Freedom from biochemical failure[21] (FFBF)<br><br>Kaplan-Meier estimate, % (95%CI)<br><br>Hazard ratio (95%CI) | 5 years<br>HDRPB: 79.8% (74.3%-85.0%)<br>EBRT: 70.9% (65.4%-76.0%)<br><br>10 years<br>HDRPB: 69.2% (59.1%-77.8%)<br>EBRT:32.8% (18.6%-46.9%)<br><br>HR=0.59 (0.43-0.81) p=0.0011 | 5 | Direct | The 344 matched EBRT controls were drawn from a total of 1107 EBRT cases. All patients were intermediate or high risk (NCCN).<br>The study was designed to have a power of 0.81 to show a 6-year improvement in FFBF of 10% (from 65% to 75%). Median f/u was between 4 years 10 months and 5 years 8 months for different outcomes.<br>EBRT was given to a total of 74 Gy in 2Gy fractions which is the current NICE recommended minimum (NICE 2014b).59% of patients received ADT; NICE recommends that radiotherapy and ADT should be offered together. |

[21] Biochemical failure defined as PSA nadir + 2 ng/mL

| a) Use of High dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| | | appears to be by patient choice<br><br>Significant differences in:<br>Age[20]: HDRPB 67 yrs; EBRT 69 yrs; p=0.037<br><br>Median clinical f/u HDRPB 68.2m; EBRT 60.7 m: p=0.003<br><br>Median PSA f/u: HDRPB 62.5m; EBRT 58.5m; p=0.006<br><br>No significant differences in PSA, GS, T stage, and presence and severity | 59% in both groups also received ADT | Primary<br><br>Clinical effectiveness | Freedom from metastases<br><br>% (95%CI) | 5 years<br>HDRPB: 90.0% (85.9%-93.3%)<br>EBRT 91.0% (87.3%-94.9%)<br><br>p=0.27 | | | The authors concluded that HDRPB led to improved FFBF, but with increased urinary toxicity. This finding should be viewed as only moderately reliable. There is a risk of bias due to the retrospective design and matched control methodology. There were significant differences in age and length of follow-up between treatment groups but no significant differences in indicators of risk or comorbidity reported. Toxicity data was not collected prospectively and toxicity outcomes were based on retrospective analysis of requirement for interventions for urethral stricture. The treatment approaches changed over the time of the study and differ in some respects from current practice. |
| | | | | Primary<br><br>Safety | Urethral stricture[22]<br><br>Cumulative 5-year incidence, % (95%CI)<br><br>Hazard ratio (95%CI) | Grade 3 stricture<br>HDRPB: 11.8% (8.1%-16.5%)<br>EBRT 0.3% (0%-0.9%)<br>p<0.0001<br><br>Grade 2 or grade 3 stricture (combined incidence)<br>HDRPB: 16.8% (12.6%-22.1%),<br>EBRT: 1.9% (0.6%-3.6%)<br><br>HR=10.8 (4.6-25.2)<br>p<0.0001 | | | |

[20] Not stated whether mean or median

[22] Not recorded prospectively. Defined as Grade 3: stricture requiring operative intervention; Grade 2: stricture requiring catheterization or dilatation.

| a) Use of High dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer | | | | | | | | | |
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| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| | | of medical comorbidity | | | | | | | |
| Hoskin et al 2012 | P1<br><br>RCT<br><br>Single centre, UK | n=216<br><br>Randomised to:<br>EBRT n=106<br>HDRPB n=110<br><br>Median age 70yrs<br><br>Risk group, HDRPBvs EBRT:<br>Low: 2%vs7%<br>Intermediate : 44%vs40%<br>High: 54%vs53% | Patients stratified by tumour stage, PSA, Gleason score and androgen deprivation therapy, then randomised to either:<br><br>HDRPB: EBRT to 35.75 Gy in 13 fractions followed by a HDRBT boost of 2x8.5 Gy in 24 h<br><br>EBRT: total dose of 55 Gy | Primary<br><br>Clinical effectiveness | Biochemical relapse-free survival (RFS) [23]<br><br>Kaplan-Meier estimates, % | HDRPB<br>5yrs: 75% 7yrs: 66%<br>10yrs: 46%<br>EBRT:<br>5yrs: 61% 7yrs: 48%<br>10yrs: 39%<br>p=0.04 | 9 | Direct | 93% of EBRT and 98% of HDRPB patients had intermediate or high risk prostate cancer (NCCN classification)<br><br>Patients were randomised using a 'balanced one-to-one randomisation' following stratification. No blinding was used for treatment delivery or follow-up assessments.<br><br>Target accrual was 214 patients to detect a 20% improvement in RFS with an a-error of 0.05 and a power of 80%. 218 were recruited; 2 were excluded from analysis, one because baseline assessment revealed metastases, one refused the allocated treatment.<br>EBRT was given to a total of 55Gy in 20 fractions which is lower than the current NICE recommended minimum of 74Gy in 37 fractions, (NICE 2014b), or the NHS England recommended dose of 60Gy in 20 fractions (NHS England 2017). Two patients randomised to HDRPB received EBRT alone. |
| | | | | Primary<br><br>Clinical effectiveness | Overall survival (OS)<br><br>Kaplan-Meier estimates, % | HDRPB<br>5yrs: 88% 7yrs: 81%<br>10yrs: 67%<br>EBRT<br>5yrs: 89% 7yrs: 88%<br>10yrs: 79%<br>p=0.2 | | | |
| | | | | Secondary<br><br>Safety | Genitourinary (GU) adverse events[24]<br><br>Incidence by 5yrs and 7yrs, Kaplan-Meier estimates | HDRPB<br>5yrs:26% 7yrs: 31%<br>EBRT<br>5yrs: 26% 7yrs:30%<br>p=0.5 | | | |

[23] RFS was taken as time to biochemical recurrence, clinical evidence of local disease, or death from any cause. Biochemical relapse was assigned to patients with a rise of 2ng/ml or more above nadir PSA and to those not meeting this criterion but who underwent salvage therapies (such as ADT, radical prostatectomy, brachytherapy, or cryosurgery). Local relapse was confirmed by imaging which was initiated in patients with rising PSA levels or with pelvic or musculoskeletal symptoms.

[24] Severe GU adverse events scored as: urinary diversion; frequency at night ≥6x; intermittent or persistent incontinence; intermittent or daily haematuria, blood clots; score 3 for urgency or dysuria.

| a) Use of High dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| | | T stage, HDRPBvsEBRT:<br>T1: 26%vs25%<br>T2: 43%vs52%<br>T3: 31%vs23%<br><br>GS, HDRPBvsEBRT:<br><7:42%vs45%<br>7: 40%vs38%<br>≥8:18%vs17%<br><br>PSA, HDRPBvs EBRT:<br><10: 32%vs34%<br>10-20: 41%vs41%<br>>20: 27%vs25% | in 20 daily fractions;<br><br>76% of patients had ADT | Secondary<br><br>Safety | Genitourinary (GU) adverse events[25]<br><br>Prevalence at 5yrs and 7yrs | HDRPB<br>5yrs: 8% 7yrs: 11%<br>EBRT<br>5yrs: 9% 7yrs:4%<br>p=1.0 (5yrs)<br>p=0.4 (7yrs) | | | 76% of all patients received ADT; NICE recommends that radiotherapy and ADT should be offered together;<br>Analysis was intention-to-treat for clinical outcomes, by treatment received for safety outcomes.<br><br>Median f/u 85 months for both treatment groups (range 8-147 months). All intervals were calculated from the date of randomisation<br><br>Overall this appears to have been a well-conducted RCT. The main source of potential bias are the inclusion of a small number of low risk patients (around 5% overall) and lack of blinding of assessment of outcomes. The findings can therefore be regarded as reasonably reliable. However the EBRT dose (55Gy) is below the current NICE recommendation of a minimum of 74Gy, or the NHS England recommended dose of 60Gy in 20 fractions (NHS England 2017).<br><br>The authors concluded that patients treated with HDRPB had an 18% increase in RFS relative to EBRT alone at 7yrs, and 7% increase at 10yrs, a significant difference, with no evidence of an increase in long-term severe urinary or rectal morbidity. RFS included biochemical or clinical relapse, or death from any cause. There was no significant difference in OS at 10yrs but the study was not powered to detect this. |
| | | | | Secondary<br><br>Safety | Urethral stricture managed surgically<br><br>Incidence by 5yrs and 7yrs, Kaplan-Meier estimates | HDRPB<br>5yrs: 6% 7yrs: 8%<br>EBRT<br>5yrs: 2% 7yrs:2%<br>p=0.1 | | | |
| | | | | Secondary<br><br>Safety | Gastrointestinal (GI) adverse events[26]<br><br>Incidence by 5yrs and 7yrs, Kaplan-Meier estimates | HDRPB<br>5yrs:7% 7yrs: 7%<br>EBRT<br>5yrs: 6% 7yrs:6%<br>p=0.8<br>(single p value reported) | | | |
| | | | | Secondary<br><br>Safety | Gastrointestinal (GI) adverse events[27]<br><br>Prevalence at 5yrs and 7yrs | HDRPB<br>5yrs: 0% 7yrs: 0%<br>EBRT<br>5yrs: 0% 7yrs: 2%<br>p=1.0<br>(single p value reported) | | | |

[25] Severe GU adverse events scored as: urinary diversion; frequency at night ≥6x; intermittent or persistent incontinence; intermittent or daily haematuria, blood clots; score 3 for urgency or dysuria.
[26] Severe GI adverse events scored as: frequency ≥6x /day; faecal consistency liquid; blood loss intermittent or daily, gross haemorrhage; rectal discharge intermittent or persistent requiring surgical treatment
[27] Severe GI adverse events scored as: frequency ≥6x /day; faecal consistency liquid; blood loss intermittent or daily, gross haemorrhage; rectal discharge intermittent or persistent requiring surgical treatment

| b) Use of High dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | | | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| Lennernas et al 2015 | P1<br><br>RCT<br><br>Five centres, Sweden<br><br>Recruited 1996-2001 | n=89<br><br>Risk group not stated<br>Patients had localized/locally advanced prostate cancer, T1b–T3a, N0, M0, PSA ≤50 ng/ml<br><br>HDRPB: n=44<br>RP: n=45<br><br>HDRPB vs RP:<br>Median age: 66 vs 64 yrs<br>T1: 39% vs 40%<br>T2: 36% vs 38% | HDRPB: HDRBT 2x10Gy plus EBRT: 25x2 Gy<br><br>RP: radical prostatectomy (nerve-sparing)<br><br>All patients had 6 months Androgen blockade | Primary<br><br>Safety | HRQoL (function) using EORTC QLQ-C33[28] subscale score at randomisation / 24 months (Range 0-100, higher score indicates better QoL)<br><br>For scale abbreviations see footnote | | HDRPB | RP | 6 | Direct | The researchers had planned to randomise 360 patients in order to evaluate impact on survival. Three amendments were made to the study protocol. It was reported to be difficult to recruit patients after the third amendment and the study was closed in April 2002 when 89 patients had been recruited. No further details were given about reasons for study closure.<br><br>Randomisation was done centrally by telephone.<br><br>Risk categories were not reported. However the inclusion criteria suggest many of the patients may have met criteria for intermediate or high risk.<br><br>Patients were followed up 6-monthly for the first 2 years then annually. Mortality was ascertained in 2011 from the Swedish deaths registry. HRQoL was assessed before randomisation and 12 and 24 months after randomisation. Questionnaires were completed by 75%, 85% and 85% of patients at the 3 time points respectively. Items were reported from the EORTC QLQ-C33 (in relation to HRQoL, function and symptoms) and an additional prostate cancer-specific questionnaire assessing urinary, bowel and sexual function. No further information was provided about this questionnaire. Not all items were reported in the paper, but there was no difference between treatment groups in any of the measures of HRQoL |
| | | | | | | Phy | 95/94 | 97/96 | | | |
| | | | | | | Role | 96/96 | 92/97 | | | |
| | | | | | | Em* | 78/87 | 81/88 | | | |
| | | | | | | Cog | 89/88 | 88/87 | | | |
| | | | | | | Sc# | 92/83 | 92/90 | | | |
| | | | | | | Glob | 80/75 | 82/77 | | | |
| | | | | | | No significant differences between treatment groups<br><br>*Overall significant improvement over time, p=0.0005<br>#Overall significant deterioration over time, p=0.0051 | | | | | |
| | | | | Primary<br><br>Safety | HRQoL (symptoms) using EORTC QLQ-C33[29] subscale score at randomisation / 24 months | | HDRPB | RP | | | |
| | | | | | | Fat | 11/12 | 14/13 | | | |
| | | | | | | Pain | 10/14 | 7/8 | | | |
| | | | | | | Insm | 13/8 | 7/9 | | | |
| | | | | | | Con | 4/3 | 1/3 | | | |
| | | | | | | Dia | 6/9 | 2/3 | | | |

[28] EORTC QLQ-C33: European Organization of Research and Treatment of Cancer Quality of Life Questionnaire C33 comprises 33 items incorporating five single-item scales and nine multi-item scales evaluating function (physical, role, cognitive, emotional, and social dimensions), symptoms (fatigue, pain, nausea/vomiting, sleeping problems, constipation, appetite loss, dyspnoea, diarrhoea), as well as global health and QoL.
Abbreviations for scales reported: Phy=Physical functioning; Role= Role functioning; Em = emotional functioning; Cog= cognitive functioning; Sc = social functioning; Glob = Global quality of life.

[29] Abbreviations for scales reported: Fat= Fatigue; Insm = insomnia; Con= constipation; Dia= diarrhoea.

| b) Use of High dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate-and high-risk localised prostate cancer | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| | | T3: 7% vs 9%<br>Unknown T: 18% vs 13%<br><br>No significant differences between groups | | | (Range 0-100, higher score indicates worse symptoms)<br><br>For scale abbreviations see footnote | No significant differences between treatment groups | | | reported. The findings from 5 additional scales from the urinary, bowel and sexual function questionnaire have not been included here because there were reported to be no significant changes over time or between groups, but no p values were reported.<br><br>The authors concluded that HDRPB and RP appeared to be comparable in the measured outcomes, and that it was not possible to draw any conclusion on the efficacy of the two treatments due to insufficient power of the study. The information provided by this study is of limited value because of its small size and lack of power, despite being designed as a RCT. There was a reasonably good level of follow-up for the HRQoL measures, but this was only up to 2 years. Identification of deaths through the national deaths registry may have led to under-ascertainment. |
| | | | | Primary<br><br>Safety | Urinary incontinence[30]<br><br>% at randomisation / 24 months reporting<br>1=Not at all;<br>2=Little;<br>3=Quite a bit;<br>4=Very much. | HDR PB / RP<br>1: 76/61 / 83/45<br>2: 17/29 / 14/39<br>3: 7/5 / 0/11<br>4: 0/5 / 3/5<br><br>No significant differences between treatment groups. Overall significant deterioration over time, p=0.0011 | | | |
| | | | | Primary<br><br>Safety | Erectile problems[31]<br><br>% at randomisation / 24 months reporting<br>1=Not at all;<br>2=Little;<br>3=Quite a bit;<br>4=Very much. | HDR PB / RP<br>1: 21/3 / 31/5<br>2: 32/11 / 36/5<br>3: 32/27 / 22/16<br>4: 15/59 / 11/74<br><br>No significant differences between treatment groups. | | | |

[30] Reported using a prostate cancer-specific HRQoL questionnaire consisting of 20 items which was developed in Gothenburg, Sweden, to gather information on specific problems experienced with respect to bowel, urinary tract, and sexual functions.

[31] Reported using a prostate cancer-specific HRQoL questionnaire consisting of 20 items which was developed in Gothenburg, Sweden, to gather information on specific problems experienced with respect to bowel, urinary tract, and sexual functions

| b) Use of High dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| | | | | | | Overall significant deterioration over time, p<0.0001 | | | |
| | | | | Primary<br><br>Clinical effectiveness | Mortality at least 10 years after randomisation (number of deaths) | Deaths due to prostate cancer<br>HDRPB: 2<br>RP: 6<br><br>Deaths due to other causes<br>HDRPB:7<br>RP: 6<br><br>Significance of differences not reported | | | |
| Noda et al 2011 | P1<br><br>Retrospective comparison of 2 treatment cohorts treated between 2000-2004<br><br>Single centre, Japan | n=150<br>Low, intermediate and high risk prostate cancer.<br><br>Significant difference between groups in T stage: HDRPB vs RP:<br>T1c+T2a: 73%vs88% p=0.029<br><br>No other significant differences reported: | HDRPB: EBRT 50Gy in 25 fractions plus HDRBT 15-18Gy in 2 fractions<br><br>RP: radical prostatectomy (no further details)<br><br>HDRPB: n=59<br>RP: n=91<br><br>Treatment allocation was patient choice.<br><br>None received ADT as part of | Primary<br><br>Clinical effectiveness | Biochemical failure-free control rate (BFFCR)[32] [33] | Whole cohort, 3 yrs:<br>HDRPB: 92%<br>RP: 72%<br>Whole cohort, 5 yrs:<br>HDRPB: 85%<br>RP: 72%<br>p<0.0012<br><br>Intermediate risk, 3 yrs:<br>HDRPB:92%<br>RP:73%<br>Intermediate risk, 5 yrs<br>HDRPB:92%<br>RP:73%<br>p<0.0492<br><br>High risk, 3 yrs:<br>HDRPB:94%<br>RP:45%<br>High risk, 5 yrs:<br>HDRPB:72%<br>RP:45% | 4 | Direct | Median f/u was 62 months (range 48-108) for HDRPB and 64 months (42-112) for RP.<br><br>Low risk was defined as all of PSA≤10ng/ml, T1c-T2a, and GS≤6. Any patient with one indicator higher than these thresholds was considered intermediate risk; any with two or more indicators higher was considered high risk. The cut-off between low and intermediate risk is therefore similar to NCCN and NICE, although a patient with two low risk indicators according to the Noda et al classification might meet the NICE or NCCN definition of high risk if the third was above their high risk threshold. The cut-off between intermediate and high risk in the Noda et al classification is likely to be lower than both NCCN and NICE. The authors did not state the numbers of patients in each risk group.<br><br>Follow-up of HDRPB and RP patients was carried out by different clinicians, introducing risk of bias due to possible differences in approach. No further details were provided about the RP patients beyond |

[32] biochemical failure defined as nadir PSA + 2ng/ml

[33] It should be noted that the intermediate and high risk categories do not correspond to those used by NCCN or NICE. Numbers in different risk groups were not stated.

| b) Use of High dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate-and high-risk localised prostate cancer | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| | | HDRPB vs RP:<br>Age≤70yrs: 27% vs43% p=0.058<br><br>GS≤6: 59%vs65%<br>GS≥7: 41%vs35% p=0.604<br><br>PSA≤10: 42%vs52%<br>PSA>10: 58%vs48% p=0.316 | initial treatment | | | p<0.0073 | | | the comparison of basic characteristics. None of the HDRPB patients received ADT as part of their initial treatment; NICE recommends that radiotherapy and ADT should be offered together.<br><br>The authors reported better BFFCR for patients receiving HDRPB vs RP and concluded that the study confirmed efficacy and safety of HDRPB. The findings must be viewed with caution due to the sources of potential bias including the retrospective analysis, unmatched cohorts, possible differences in assessment between the groups, limited information about the RP group, and other likely confounders. |

| c) Use of High dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| Kishan et al 2017 | P1<br><br>Retrospective analysis comparing 3 cohorts treated between 2000 | n=487<br><br>High risk All had biopsy GS 9-10<br><br>HDRPB: n=87, of whom | HDRPB: median equivalent dose 88.7Gy (IQR 81.9-98.9Gy). 75(86.2%) had ADT, median duration 8m.<br>HDRBT: 24Gy in 6 fractions | Primary<br><br>Clinical effectiveness | Overall survival (OS)<br><br>Kaplan-Meier estimate, % (95%CI)<br><br><br><br>Hazard ratio (95%CI) | 5yrs:<br>HDRPB: 84.7%<br>EBRT: 79.9%<br>RP: 90.3%<br><br>10yrs:<br>HDRPB: 59.2%<br>EBRT: 65.3%<br>RP: 72.1%<br><br>HDRPBvsEBRT:<br>HR: 0.99 (0.58-1.98) | 5 | Direct | This study retrospectively compared outcomes for patients with high risk prostate cancer and biopsy GS of 9-10; 21.2% of the RP patients were subsequently found to have pathological GS of 7 or 8.<br><br>Median f/u (from the end of local treatment) was 4.6yrs (all patients); 4.2yrs (EBRT), 6.5yrs (HDRPB), 4.9yrs (RP). Differences between groups were not significant. |

| c) Use of High dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| | and 2013<br><br>3 treatment centres, USA | EBRT+HDRBT: n=84, and EBRT+LDRBT: n=3<br>EBRT: n=230<br>RP: n=170<br><br>Median age:<br>HDRPB: 70yrs<br>EBRT: 70yrs<br>RP: 62 yrs.<br>Significant differences between:<br>RPvsHDRPB: p<0.0001<br>RPvsEBRT: p<0.0001<br><br>Median iPSA:<br>HDRPB: 11.7<br>EBRT: 9.76<br>RP: 7.8<br>Significant differences between:<br>RPvsHDRPB: p<0.001<br>RPvsEBRT: p<0.01<br><br>Clinical stage: | LDRBT: 108Gy using $^{125}$I.<br><br>EBRT: median equivalent dose 76.4Gy (IQR 65-80Gy). 216(93.9%) had ADT, median duration 24m.<br><br>RP: 34% robotic-assisted. 9 (5.3%) received adjuvant ADT. | | | p=0.98<br><br>HDRPBvsRP:<br>HR: 1.06 (0.53-2.12)<br>p=0.86 | | | Outcomes were defined by intervals from the end of treatment.<br>Kaplan-Meier survival analysis was used to evaluate outcomes at 5yrs and 10yrs follow-up.<br>Multivariate Cox analysis was used to estimate HRs of these outcomes between treatment cohorts (adjusted for age, GS, clinical stage, iPSA, year of treatment, local salvage, systemic salvage).<br><br>There were a number of potential sources of bias relating to patient characteristics, approaches to treatment and measurement of outcomes.<br>Patients in the HDRPB group had significantly higher clinical stage than both the RP group (p<0.0001) and the EBRT group (p<0.05). Patients in the HDRPB group included 84 who received HDRBT and 3 who received LDRBT; results were not presented separately for the two groups.<br>There were significant differences in receipt of ADT; 5.3% of RP patients received adjuvant ADT; 86.2% of HDRPB received ADT for median 8m; 93.9% of EBRT patients received ADT for median 24m.<br>One treatment centre treated only HDRPB patients; one treated both EBRT and RP, and one provided all 3 treatment modalities.<br>Biochemical recurrence was defined at a lower threshold for RP patients than for patients receiving HDRPB or EBRT.<br><br>The authors concluded that patients treated with HDRPB had significantly better DM free survival than those treated with either EBRT alone or RP. They also concluded that there were no differences in OS or PCSM between the three treatment cohorts. They did not include the BR findings in their conclusions as they considered the difference in definition of BR between the RP and HDRPB and EBRT groups introduced bias. |
| | | | | Primary<br><br>Clinical effectiveness | Prostate cancer-specific mortality (PCSM)<br><br>Kaplan-Meier estimate, % (95%CI)<br><br>Hazard ratio (95%CI) | 5yrs:<br>HDRPB: 4.4%<br>EBRT: 8.4%<br>RP: 8.3%<br><br>10yrs:<br>HDRPB: 11.9%<br>EBRT: 19.5%<br>RP: 21.5%<br><br>HDRPBvsEBRT:<br>HR: 0.64 (0.24-1.71)<br>p=0.37<br><br>HDRPBvsRP:<br>HR: 0.48 (0.16-1.4)<br>p=0.18 | | | |
| | | | | Primary<br><br>Clinical effectiveness | Biochemical recurrence[34] (BR)<br><br>Kaplan-Meier estimate, % (95%CI)<br><br>Hazard ratio (95%CI) | 5yrs:<br>HDRPB: 17.1%<br>EBRT: 28.2%<br>RP: 73.6%<br><br>10yrs:<br>HDRPB: 30.0%<br>EBRT: 39.7%<br>RP: 83.8%<br><br>HDRPBvsEBRT:<br>HR: 0.76 (0.44-1.32)<br>p=0.33<br><br>HDRPBvsRP:<br>HR: 0.16 (0.09-0.28) | | | |

[34] Defined as: for RP patients, a postoperative PSA of ≥0.2ng/ml or initiation of salvage therapy. For HDRPB and EBRT patients, PSA ≥2ng/ml above nadir or initiation of salvage therapy.

| c) Use of High dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study reference** | **Study Design** | **Population characteristics** | **Intervention** | **Outcome measure type** | **Outcome measures** | **Results** | **Quality of Evidence Score** | **Applicability** | **Critical Appraisal Summary** |
| | | Significantly higher in HDRPB than RP (p<0.0001). Significantly higher in HDRPB than EBRT (p<0.05). Significantly higher in EBRT than RP (p<0.0001). | | | | p<0.0001 | | | |
| | | | | Primary<br><br>Clinical effectiveness | Distant metastases[35] (DM)<br>Kaplan-Meier estimate, % (95%CI)<br><br>Hazard ratio (95%CI) | 5yrs:<br>HDRPB+BT:5.4%<br>EBRT: 21.3%<br>RP: 20.9%<br><br>10yrs:<br>HDRPB: 10.2%<br>EBRT: 33.3%<br>RP: 38.5%<br><br>HDRPBvsEBRT:<br>HR: 0.30 (0.12-0.72)<br>p=0.008<br><br>HDRPBvsRP:<br>HR: 0.23 (0.09-0.6)<br>p=0.003 | | | The findings must be viewed as only moderately reliable due to the sources of potential bias; the retrospective analysis, unmatched cohorts, differences between the groups in characteristics and treatment approaches, and other likely confounders. |

**Abbreviations**

ADT: Androgen deprivation therapy; bPFS: Biochemical progression-free survival; BT: Brachytherapy; CI: Confidence Interval; DE-EBRT: DM: Distant metastases; Dose-escalated external beam radiotherapy; EBRT: external beam radiation therapy; f/u: follow-up; GI: Gastrointestinal; GS: Gleason score; GU: genitourinary; Gy: Gray; HDRBT: High dose rate brachytherapy; HDRPB: High dose rate prostate brachytherapy boost; HRQoL: Health-related quality of life; IMRT: Intensity-modulated radiotherapy ; LDRBT: Low dose rate brachytherapy; LDRPB: Low dose rate prostate brachytherapy ; MFS: Metastasis-free survival; NCCN: National Comprehensive Cancer Network; NICE: National Institute of Health and Care Excellence; OS: Overall survival; PSA: Prostate specific antigen; QALY: Quality Adjusted Life Year; RP: Radical prostatectomy

[35] Distant metastases were classified as imaging evidence of lesions that were clinically or pathologically diagnosed as metastatic.

## 8 Grade of Evidence Table

For abbreviations see list after tables

| a) Use of High dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer | | | | | |
|---|---|---|---|---|---|
| **Outcome Measure** | **Reference** | **Quality of Evidence Score** | **Applicability** | **Grade of Evidence** | **Interpretation of Evidence** |
| Overall survival | Hoskin 2012 | 9 | Direct | B | Overall survival (OS) is the proportion of subjects still alive at a defined time point.<br><br>Hoskin et al reported OS at 5, 7 and 10 yrs respectively of 88%, 81% and 67% in the group receiving HDRPB and 89%, 88% and 79% in those receiving EBRT. There was no statistically significant difference between the groups (p=0.2).<br><br>An improvement in OS would extremely important for patients, their families and clinicians. Both treatment groups had reasonably high rates of OS, but the study did not demonstrate that either radiotherapy treatment was more beneficial.<br><br>This appears to have been a well-conducted RCT whose results can be regarded as reliable. However it was not powered to detect differences in OS. The EBRT dose used for the comparator group (55Gy) is below the current NICE recommendation of a minimum of 74Gy or the NHS England recommended dose of 60Gy in 20 fractions, and only 76% of all patients received ADT. |
| Overall mortality | Wedde 2018 | 4 | Direct | C | Overall mortality (OM) is the proportion of patients who have died from any cause at a defined time point.<br><br>Wedde et al reported that OM at 10 yrs was 12.92% (42/325) in the group receiving HDR-EBRT and 23.31% (69/296) in the group receiving EBRT alone, a significant difference (p=0.02). The main contributor to the difference between groups was the number of prostate cancer deaths (see below).<br><br>Reducing OM would be extremely important for patients, their families and clinicians. This study suggests the group receiving HDR-EBRT were around half as likely to have died due to any cause than those receiving EBRT alone.<br><br>This was a retrospective analysis of 2 treatment cohorts treated at a number of different treatment centres. All patients were high risk. There were a number of potential sources of bias, including the retrospective design, differences in approach between treatment centres, differences between the treatment groups in provision of ADT, and baseline differences between the cohorts. The findings can therefore be regarded as only moderately reliable. |
| Prostate cancer-specific mortality | Wedde 2018 | 4 | Direct | C | Prostate cancer-specific mortality (PCSM) is the proportion of patients who have died due to prostate cancer at a defined time point.<br><br>Wedde et al reported that PCSM at 5 and 10 yrs was 1% and 2.5% (7/325) respectively in the group receiving HDR-EBRT and 3.1% and 8.2% (25/296) respectively in the group receiving EBRT alone, a statistically significant difference (p<0.01). |

| a) Use of High dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer | | | | | |
|---|---|---|---|---|---|
| **Outcome Measure** | **Reference** | **Quality of Evidence Score** | **Applicability** | **Grade of Evidence** | **Interpretation of Evidence** |
| | | | | | Reducing deaths due to prostate cancer would be extremely important for patients, their families and clinicians. This study suggests that the group receiving HDR-EBRT were over three times less likely to have died due to prostate cancer than those receiving EBRT alone.<br><br>This was a retrospective analysis of 2 treatment cohorts treated at a number of different treatment centres. All patients were high risk. There were a number of potential sources of bias, including the retrospective design, differences in approach between treatment centres, differences between the treatment groups in provision of ADT, and baseline differences between the cohorts. The findings can therefore be regarded as only moderately reliable. |
| Biochemical relapse-free survival | Hoskin 2012 | 9 | Direct | B | Biochemical relapse-free survival (RFS) is the proportion of patients without relapse at a defined time point. Relapse was defined as biochemical recurrence (patients with a rise of 2ng/ml or more above nadir PSA, and those not meeting this criterion but who underwent salvage therapies such as ADT, radical prostatectomy, brachytherapy, or cryosurgery); clinical evidence of local disease (confirmed by imaging which was initiated in patients with rising PSA levels or with pelvic or musculoskeletal symptoms); or death from any cause.<br><br>Hoskin et al reported RFS at 5, 7 and 10 yrs respectively of 75%, 66% and 46% in the group receiving HDRPB and 61%, 48% and 39% in those receiving EBRT alone. The difference between the groups was statistically significant (p=0.04).<br><br>An improvement in RFS would be extremely important for patients, their families and clinicians as biochemical relapse reflects disease progression and is likely to be associated with greater morbidity and mortality. This study suggests that around a third more patients receiving HDRPB were likely to have avoided biochemical relapse at 7 years than those receiving EBRT alone, but the difference had narrowed by 10 years.<br><br>This appears to have been a well-conducted RCT whose results can be regarded as reliable. The EBRT dose used for the comparator group (55Gy) is below the current NICE recommendation of a minimum of 74Gy or the NHS England recommended dose of 60Gy in 20 fractions, and only 76% of all patients received ADT. |
| Freedom from biochemical failure | Khor 2013 | 5 | Direct | C | Freedom from biochemical failure (FFBF) is the proportion of patients without biochemical failure (defined as a rise of 2ng/ml or more above PSA nadir) at a defined time point.<br><br>Khor et al reported FFBF at 5 and 10yrs respectively of 79.8% and 69.2% in the group receiving HDRPB and 70.9% and 32.8% in the group receiving EBRT alone. The difference between treatment groups was statistically significant (p=0.0011).<br><br>An improvement in FFBF would be extremely important for patients, their families and clinicians as biochemical failure reflects disease progression and is likely to be associated with greater morbidity and mortality. This study suggests that over twice as many patients treated with HDRPB were free from biochemical failure at 10 years compared with those treated with EBRT alone.<br><br>This was a retrospective analysis of 2 matched cohorts. All patients were intermediate or high risk. The EBRT dose received by the EBRT-alone group was in line with the current NICE |

| a) Use of High dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer | | | | | |
|---|---|---|---|---|---|
| **Outcome Measure** | **Reference** | **Quality of Evidence Score** | **Applicability** | **Grade of Evidence** | **Interpretation of Evidence** |
| | | | | | recommendation, but only 59% of all patients received ADT. There were a number of potential sources of bias, including the retrospective design, changes in treatment approaches over time, and baseline differences between the cohorts in age and length of follow-up, although there were no significant differences in the indicators of risk or comorbidity reported.. The findings can therefore be regarded as only moderately reliable. |
| Freedom from metastases | Khor 2013 | 5 | Direct | C | Freedom from metastases (FFM) is the proportion of patients without metastases (not further defined in this study) at a defined time point.<br><br>Khor et al reported FFM at 5yrs of 90.0% in the group receiving HDRPB and 91.0% in the group receiving EBRT alone. The difference between treatment groups was not statistically significant (p=0.27).<br><br>A reduction in metastases would be extremely important for patients, their families and clinicians as they reflect disease progression and are likely to be associated with greater morbidity and mortality. This study suggests no difference between the groups treated with HDRPB or EBRT alone in the proportion free from metastases at 5 years.<br><br>This was a retrospective analysis of 2 matched cohorts. All patients were intermediate or high risk. The EBRT dose received by the EBRT-alone group was in line with the current NICE recommendation, but only 59% of all patients received ADT. There were a number of potential sources of bias, including the retrospective design, changes in treatment approaches over time, and baseline differences between the cohorts in age and length of follow-up, although there were no significant differences in the indicators of risk or comorbidity reported. The findings can therefore be regarded as only moderately reliable. |
| Genitourinary adverse events | Hoskin 2012 | 9 | Direct | B | Genitourinary (GU) adverse events as reported in this outcome were defined as: urinary diversion; frequency at night ≥6 times; intermittent or persistent incontinence; intermittent or daily haematuria, blood clots; score 3 for urgency or dysuria.<br><br>Hoskin et al reported the cumulative incidence of GU adverse events by 5 and 7 yrs respectively of 26% and 31% in the group receiving HDRPB and 26% and 30% in those receiving EBRT alone. The difference between the groups was not statistically significant (p=0.5). They also reported the prevalence of GU adverse events at 5 and 7yrs respectively of 8% and 11% in the group receiving HDRPB and 9% and 4% in those receiving EBRT alone. The differences were not statistically significant (p=1.0 (5yrs), p=0.4 (7yrs)).<br><br>Almost a third of all patients experienced GU adverse events which can cause significant morbidity and reduction in quality of life, so a reduction would be important for patients, their families and clinicians. This study suggests no difference in GU adverse events between patients receiving HDRPB and those receiving EBRT alone.<br><br>This appears to have been a well-conducted RCT whose results can be regarded as reliable. The adverse event outcomes reported here were analysed by treatment received rather than intention-to treat. The EBRT dose used for the comparator group (55Gy) is below the current NICE |

| a) Use of High dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer | | | | | |
|---|---|---|---|---|---|
| **Outcome Measure** | **Reference** | **Quality of Evidence Score** | **Applicability** | **Grade of Evidence** | **Interpretation of Evidence** |
| | | | | | recommendation of a minimum of 74Gy or the NHS England recommended dose of 60Gy in 20 fractions, and only 76% of all patients received ADT. |
| Gastrointestinal adverse events | Hoskin 2012 | 9 | Direct | B | Gastrointestinal (GI) adverse events as reported in this outcome were defined as frequency ≥6x /day; faecal consistency liquid; blood loss intermittent or daily, gross haemorrhage; rectal discharge intermittent or persistent requiring surgical treatment.<br><br>Hoskin et al reported the cumulative incidence of GI adverse events by 5 and 7 yrs respectively of 7% and 7% in the group receiving HDRPB and 6% and 6% in those receiving EBRT alone. The difference between the groups was not statistically significant (p=0.8). They also reported the prevalence of GI adverse events at 5 and 7yrs respectively of 0% and 0% in the group receiving HDRPB and 0% and 2% in those receiving EBRT alone. The differences were not statistically significant (p=1.0).<br><br>While the overall incidence of GI adverse events was relatively low in both groups, a reduction would be important for patients, their families and clinicians as they can cause significant morbidity and reduction in quality of life. This study suggests no difference in GI adverse events between patients receiving HDRPB and those receiving EBRT alone.<br><br>This appears to have been a well-conducted RCT whose results can be regarded as reliable. The adverse event outcomes reported here were analysed by treatment received rather than intent-to treat. The EBRT dose used for the comparator group (55Gy) is below the current NICE recommendation of a minimum of 74Gy or the NHS England recommended dose of 60Gy in 20 fractions, and only 76% of all patients received ADT. |
| Urethral stricture | Hoskin 2012 | 9 | Direct | B | A urethral stricture is a narrowing of the urethra which may result in difficulty in passing urine and may require management by catheterisation or surgical intervention.<br><br>Hoskin et al reported the cumulative incidence of urethral stricture requiring surgical management by 5 and 7 yrs respectively of 6% and 8% in the group receiving HDRPB and 2% and 2% in those receiving EBRT alone. The difference between the groups was not statistically significant (p=0.1).<br><br>While the overall incidence of urethral stricture was relatively low in both groups, a reduction would be important for patients, their families and clinicians as they can cause significant morbidity and reduction in quality of life and require surgical intervention. This study suggests no difference in the incidence of urethral stricture requiring surgical management between patients receiving HDRPB and those receiving EBRT alone.<br><br>This appears to have been a well-conducted RCT whose results can be regarded as reliable. The adverse event outcomes reported here were analysed by treatment received rather than intent-to treat. The EBRT dose used for the comparator group (55Gy) is below the current NICE recommendation of a minimum of 74Gy or the NHS England recommended dose of 60Gy in 20 fractions, and only 76% of all patients received ADT. |
| | Khor 2013 | 5 | Direct | | |
| Expected lifetime cost of treatment | Vu 2018 | 3 | Direct | C | The expected lifetime cost of treatment as reported in this study included estimates of the US cost of initial treatment and of treatment required for disease progression and complications. |

| a) Use of High dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer | | | | | |
|---|---|---|---|---|---|
| **Outcome Measure** | **Reference** | **Quality of Evidence Score** | **Applicability** | **Grade of Evidence** | **Interpretation of Evidence** |
| | | | | | Vu et al reported the estimated lifetime cost of treatment for their base case estimates to be US$68,696 for patients receiving HDRPB and US$114,944 for patients receiving IMRT alone. For alternative case 1 (assuming worse outcomes, higher toxicity and greater costs for brachytherapy than the base case) their estimated lifetime costs were US$106,143 for HDRPB and US$102.238 for IMRT alone. For alternative case 2 (assuming better outcomes, lower toxicity and lower costs for brachytherapy than the base case) their estimated lifetime costs were US$42,817 for HDRPB and US$111,738 for IMRT alone. The statistical significance of differences was not reported. Cost-effectiveness was not reported for the base case.<br><br>A reduction in treatment costs would be important for those paying for care, although this would need to be linked with an analysis of treatment outcomes to ascertain cost-effectiveness. The authors concluded that the lifetime treatment cost of their standard approach to treatment was over 50% higher for patients receiving IMRT alone compared with HDRPB. However this relative difference changed when they changed the assumptions they made about approaches to treatment and treatment outcomes.<br><br>This study used a cost-effectiveness model based on assumptions which were drawn from a range of sources. Assumptions about disease progression, outcomes and toxicity were based on the findings of the ASCENDE-RT trial (Morris et al 2017). ASCENDE-RT compared LDRPB with DE-EBRT while Vu et al aimed to compare HDRPB with IMRT, and no evidence was provided demonstrating that outcomes of these treatment approaches would be the same. The use of ASCENDE-RT as a source for model assumptions therefore appears questionable. Other published studies were also used for other model assumptions. Costs were US costs, using Medicare reimbursement and other sources, so may not reflect actual treatment costs and are not generalisable to the UK. The findings of this study should therefore be regarded as unreliable. |
| Expected QALYs | Vu 2018 | 3 | Direct | C | QALYs (quality adjusted life years) are a way of assessing treatment benefits taking into account both length and quality of life.<br><br>Vu et al (2018) reported the estimated QALYs for their base case estimates to be 10.8yrs for patients receiving HDRPB and 9.3yrs for patients receiving IMRT alone. For alternative case 1 (assuming worse outcomes, higher toxicity and greater costs for brachytherapy than the base case) their estimated QALYs were 9.49yrs for HDRPB and 9.3yrs for IMRT alone. For alternative case 2 (assuming better outcomes, lower toxicity and lower costs for brachytherapy than the base case) their estimated QALYs were 12.07yrs for HDRPB and 9.3yrs for IMRT alone. The statistical significance of differences was not reported. Cost-effectiveness was not reported for the base case.<br><br>An improvement in both length and quality of life as a result of treatment would be extremely important for patients, their families and clinicians, although this would need to be linked with an analysis of treatment costs to ascertain cost-effectiveness. The authors concluded that using their assumptions based on a standard approach to treatment, patients receiving HDRPB could expect 1.5 more QALYs than those receiving IMRT alone. This suggests a benefit in both length and quality of life for the HDRPB group. They did not report the cost-effectiveness (i.e. the cost per QALY) of the standard approach to treatment. The difference between the treatment groups |

| a) Use of High dose rate brachytherapy boost with EBRT vs EBRT for intermediate- and high-risk localised prostate cancer | | | | | |
|---|---|---|---|---|---|
| **Outcome Measure** | **Reference** | **Quality of Evidence Score** | **Applicability** | **Grade of Evidence** | **Interpretation of Evidence** |
| | | | | | changed when they changed the assumptions they made about approaches to treatment and treatment outcomes.<br><br>This study used a cost-effectiveness model based on assumptions which were drawn from a range of sources. Assumptions about disease progression, outcomes and toxicity were based on the findings of the ASCENDE-RT trial (Morris et al 2017). ASCENDE-RT compared LDRPB with DE-EBRT while Vu et al aimed to compare HDRPB with IMRT, and no evidence was provided demonstrating that outcomes of these treatment approaches would be the same. The use of ASCENDE-RT as a source for model assumptions therefore appears questionable. Other published studies were also used for other model assumptions. The findings of this study should therefore be regarded as unreliable. |

| b) Use of High dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer | | | | | |
|---|---|---|---|---|---|
| **Outcome Measure** | **Reference** | **Quality of Evidence Score** | **Applicability** | **Grade of Evidence** | **Interpretation of Evidence** |
| Mortality | Lennernas 2015 | 6 | Direct | C | Mortality includes deaths due to all causes.<br><br>Lennernas et al reported that at least 10 years after randomisation there had been 2 deaths due to prostate cancer in the group treated with HDRPB and 6 in those treated with RP. At the same point there had been 7 deaths due to other causes in the group treated with HDRPB and 6 in those treated with RP. The significance of differences between groups was not reported.<br><br>A reduction in mortality would be extremely important to patients, their families and clinicians. This study reported 9 deaths (2 due to prostate cancer) in the 44 subjects treated with HDRPB and 12 deaths (6 due to prostate cancer) in the 45 subjects treated with RP at least 10 years after randomisation. They did not report whether the differences between the groups were significant.<br><br>This appears to have been a well-conducted RCT but recruited only 89 subjects, about a quarter of the total originally planned, and was significantly underpowered to detect differences between treatment groups. The subjects' risk groups were not stated. It is not possible to draw any conclusions about mortality associated with the different treatment approaches from the results presented. |
| Biochemical failure-free control rate | Noda 2011 | 4 | Direct | C | Biochemical failure-free control rate (BFFCR) is the proportion of subjects who are free of biochemical failure (defined as a rise of 2ng/ml or more above the nadir PSA level) at a defined time point.<br><br>Noda et al reported a BFFCR at 3yrs and 5yrs respectively of 92% and 85% for patients receiving HDRPB and 72% and 72% for those receiving RP. This difference was statistically significant ($p<0.0012$). This was the result for their whole cohort which included an unspecified number of low risk patients. They reported a BFFCR for the intermediate risk patients only at 3yrs and 5yrs respectively of 92% and 92% for patients receiving HDRPB and 73% and 73% for those receiving RP. This difference was statistically significant ($p<0.0492$). They also reported a BFFCR for the high risk patients only at 3yrs and 5yrs respectively of 94% and 72% for patients receiving HDRPB and 45% and 45% for those receiving RP. This difference was statistically significant ($p<0.0073$).<br><br>An improvement in BFFCR would be extremely important for patients, their families and clinicians as biochemical failure reflects disease progression and is likely to be associated with greater morbidity and mortality. Noda et al reported significant improvements in BFFCR for patients receiving HDRPB compared with those receiving RP for their whole cohort, and for intermediate and high risk subgroups. At 5 years, about 13% more of the whole cohort of HDRPB patients, 19% more of the intermediate risk HDRPB patients, and 27% more of the high risk HDRPB patients did not have biochemical failure compared with the RP patients in the same risk groups.<br><br>This study was a retrospective comparison of 2 treatment cohorts. There were significant differences between them at baseline in T stage, but no other significant differences reported. The 2 groups were managed and assessed by different groups of clinicians and very little information was provided about the RP group. Risk groups did not correspond to NCCN or NICE definitions and the numbers in each risk group were not stated. There were therefore a number of sources of potential bias and the findings of this study should be viewed with caution. |

| b) Use of High dose rate brachytherapy boost with EBRT vs radical prostatectomy for intermediate- and high-risk localised prostate cancer | | | | | |
|---|---|---|---|---|---|
| **Outcome Measure** | **Reference** | **Quality of Evidence Score** | **Applicability** | **Grade of Evidence** | **Interpretation of Evidence** |
| Health-related quality of life (function and symptoms) | Lennernas 2015 | 6 | Direct | C | Health-related quality of life (HRQoL) was measured using the European Organization of Research and Treatment of Cancer Quality of Life Questionnaire C33 (EORTC QLQ-C33). This comprises 33 items incorporating five single-item scales and nine multi-item scales evaluating function (physical, role, cognitive, emotional, and social), symptoms (fatigue, pain, nausea/vomiting, sleeping problems, constipation, appetite loss, dyspnoea, diarrhoea), and global health and QoL.<br><br>Lennernas et al (2015) reported scores for a number of the scales at randomisation and at 12 and 24 months. They found no significant difference between treatment groups in scores for physical, role, emotional, cognitive or social functioning or in global QoL. They found an overall significant improvement over time in emotional functioning (p=0.0005) and an overall significant deterioration over time in social functioning (p=0.0051). In the symptom scores, they found no significant differences between groups or over time in fatigue, pain, insomnia, constipation or diarrhoea.<br><br>HRQoL is an extremely important outcome for patients, their families and clinicians. This study found no significant differences between treatment groups in any measures of HRQoL up to 24 months after randomisation, although there was a worsening of social functioning and improvement in emotional functioning for the whole study population over time.<br><br>This appears to have been a well-conducted RCT but recruited only 89 subjects, about a quarter of the total originally planned, and was significantly underpowered to detect differences between treatment groups. The subjects' risk groups were not stated. It is not possible to draw any conclusions about differences in HRQoL associated with the different treatment approaches from the results presented. |
| Urinary and sexual function | Lennernas 2015 | 6 | Direct | C | Urinary, bowel and sexual function were assessed using a prostate cancer-specific questionnaire, but no further details were provided about this measure.<br><br>Lennernas et al (2015) reported scores for a number of items from the questionnaire at randomisation and at 12 and 24 months. They reported no significant difference between treatment groups in any of the measures, although p values were not reported. The scores for urinary incontinence and erectile problems showed an overall significant deterioration over time (urinary incontinence p=0.0011; erectile problems p<0.0001).<br><br>Urinary and sexual function are important outcomes for patients, their families and clinicians. This study found no significant differences between treatment groups, but a worsening of urinary incontinence and erectile problems for the whole study population up to 24 months after randomisation.<br><br>This appears to have been a well-conducted RCT but recruited only 89 subjects, about a quarter of the total originally planned, and was significantly underpowered to detect differences between treatment groups. The subjects' risk groups were not stated. It is not possible to draw any conclusions about differences in urinary and sexual function associated with the different treatment approaches from the results presented. |

| c) Use of High dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer | | | | | |
|---|---|---|---|---|---|
| **Outcome Measure** | **Reference** | **Quality of Evidence Score** | **Applicability** | **Grade of Evidence** | **Interpretation of Evidence** |
| Overall survival | Kishan 2017 | 5 | Direct | C | Overall survival (OS) is the proportion of subjects still alive at a defined time point.<br><br>Kishan et al (2017) reported estimated OS at 5 and 10 years respectively of 84.7% and 59.2% in the group receiving HDRPB, 79.9% and 65.3% in the group receiving EBRT, and 90.3% and 72.1% in the group receiving RP. There was no statistically significant difference in OS between the group receiving HDRPB and either of the other two treatment groups (HDRPBvsEBRT: HR=0.99 (95%CI 0.58-1.98), p=0.98; HDRPBvsRP: HR=1.06 (95%CI 0.53-2.12), p=0.8688).<br><br>An improvement in OS would extremely important for patients, their families and clinicians. The study did not demonstrate any difference in OS up to 10 years after treatment between patients receiving HDRPB and those receiving either EBRT alone or RP.<br><br>This was a retrospective analysis of 3 treatment cohorts treated at 3 different centres. All patients were high risk. There were a number of potential sources of bias, including the retrospective design, differences between treatment groups in clinical stage and receipt of ADT, and differences in treatment approaches and follow-up between treatment centres. Patients in the HDRPB group included 84 who received HDRBT and 3 who received LDRBT. The findings can therefore be regarded as only moderately reliable. |
| Prostate cancer-specific mortality | Kishan 2017 | 5 | Direct | C | Prostate cancer-specific mortality (PCSM) is the proportion of patients who have died due to prostate cancer at a defined time point.<br><br>Kishan et al (2017) reported estimated PCSM at 5 and 10 years respectively of 4.4% and 11.9% in the group receiving HDRPB, 8.4% and 19.5% in the group receiving EBRT, and 8.3% and 21.5% in the group receiving RP. There was no statistically significant difference in PCSM between the group receiving HDRPB and either of the other two treatment groups (HDRPBvsEBRT: HR=0.64 (95%CI 0.24-1.71), p=0.37; HDRPBvsRP: HR=0.48 (95%CI 0.16-1.4), p=0.18).<br><br>A reduction in deaths due to prostate cancer would be extremely important for patients, their families and clinicians. The study did not demonstrate any difference in deaths due to prostate cancer up to 10 years after treatment between patients receiving HDRPB and those receiving either EBRT alone or RP.<br><br>This was a retrospective analysis of 3 treatment cohorts treated at 3 different centres. All patients were high risk. There were a number of potential sources of bias, including the retrospective design, differences between treatment groups in clinical stage and receipt of ADT, and differences in treatment approaches and follow-up between treatment centres. Patients in the HDRPB group included 84 who received HDRBT and 3 who received LDRBT. The findings can therefore be regarded as only moderately reliable. |
| Biochemical recurrence | Kishan 2017 | 5 | Direct | C | Biochemical recurrence was defined for RP patients as a postoperative PSA of ≥0.2ng/ml or initiation of salvage therapy, and for HDRPB and EBRT patients, a PSA ≥2ng/ml above the nadir for that patient or the initiation of salvage therapy.<br><br>Kishan et al (2017) reported biochemical recurrence at 5 and 10 years respectively of 17.1% and 30.0% in the group receiving HDRPB, 28.2% and 39.7% in the group receiving EBRT, and 73.6% |

| c) Use of High dose rate brachytherapy boost with EBRT vs EBRT alone vs RP for high-risk localised prostate cancer | | | | | |
|---|---|---|---|---|---|
| **Outcome Measure** | **Reference** | **Quality of Evidence Score** | **Applicability** | **Grade of Evidence** | **Interpretation of Evidence** |
| | | | | | and 83.8% in the group receiving RP. There was no statistically significant difference in biochemical recurrence between the group receiving HDRPB and those receiving EBRT (HR=0.76 (95%CI 0.44-1.32), p=0.33). The rate of biochemical recurrence was statistically significantly lower in the group receiving HDRPB than the group receiving RP (HR=0.16 (95%CI 0.09-0.28), p<0.0001).<br><br>A reduction in biochemical recurrence would be extremely important for patients, their families and clinicians as biochemical recurrence reflects disease progression and is likely to be associated with greater morbidity and mortality. Kishan et al found that patients receiving HDRPB were about one-sixth as likely to experience biochemical recurrence up to 10 years after treatment as those receiving RP. There was no difference in biochemical recurrence between those receiving HDRPB and EBRT alone. The authors considered that the findings were subject to bias because of differences between groups in the definition of biochemical recurrence and did not include this finding in their conclusions.<br><br>This finding should be viewed with extreme caution as biochemical recurrence was defined at a lower threshold for RP patients than for patients receiving HDRPB or EBRT. This was a retrospective analysis of 3 treatment cohorts treated at 3 different centres. All patients were high risk. There were a number of potential sources of bias, including the retrospective design, differences between treatment groups in clinical stage and receipt of ADT, and differences in treatment approaches and follow-up between treatment centres. Patients in the HDRPB group included 84 who received HDRBT and 3 who received LDRBT. |
| Distant metastases | Kishan 2017 | 5 | Direct | C | Distant metastases (DM) were classified as imaging evidence of lesions that were clinically or pathologically diagnosed as metastatic.<br><br>Kishan et al (2017) reported a rate of DM at 5 and 10 years respectively of 5.4% and 10.2% in the group receiving HDRPB, 20.9% and 33.3% in the group receiving EBRT, and 20.9% and 38.5% in the group receiving RP. The rate of DM was statistically significantly lower in the group receiving HDRPB than in both the group receiving EBRT (HR=0.30 (95%CI 0.12-0.72), p=0.008) and the group receiving RP (HR=0.23 (95%CI 0.09-0.6), p=0.003).<br><br>A reduction in metastases would be extremely important for patients, their families and clinicians as they reflect disease progression and are likely to be associated with greater morbidity and mortality. Kishan et al found that up to 10 years after treatment, patients receiving HDRPB were about a third as likely to experience DM as those receiving EBRT alone, and about a quarter as likely to experience DM as those receiving RP.<br><br>This was a retrospective analysis of 3 treatment cohorts treated at 3 different centres. All patients were high risk. There were a number of potential sources of bias, including the retrospective design, differences between treatment groups in clinical stage and receipt of ADT, and differences in treatment approaches and follow-up between treatment centres. Patients in the HDRPB group included 84 who received HDRBT and 3 who received LDRBT. The findings can therefore be regarded as only moderately reliable. |

## Abbreviations

ADT: Androgen deprivation therapy; bPFS: Biochemical progression-free survival; BT: Brachytherapy; CI: Confidence Interval; DE-EBRT: Dose-escalated external beam radiotherapy; DM: Distant metastases; EBRT: external beam radiation therapy; f/u: follow-up; GI: Gastrointestinal; GS: Gleason score; GU: genitourinary; Gy: Gray; HDRBT: High dose rate brachytherapy; HDRPB: High dose rate prostate brachytherapy boost; HRQoL: Health-related quality of life; IMRT: Intensity-modulated radiotherapy ; LDRBT: Low dose rate brachytherapy; LDRPB: Low dose rate prostate brachytherapy ; MFS: Metastasis-free survival; NCCN: National Comprehensive Cancer Network; NICE: National Institute of Health and Care Excellence; OS: Overall survival; PSA: Prostate specific antigen; QALY: Quality Adjusted Life Year; RP: Radical prostatectomy

## 9 Literature Search Terms

| PICO Table | |
|---|---|
| **P – Patients / Population**<br>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 who are suitable for a general/spinal anaesthetic<br><br>[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] |
| **I – Intervention**<br>Which intervention, treatment or approach should be used? | HDR brachytherapy to prostate in combination with external beam radiotherapy to prostate +/- pelvic lymph nodes with or without androgen deprivation therapy |
| **C – Comparison**<br>What is/are the main alternative/s to compare with the intervention being considered? | Surgery (robotic assisted, laparascopic or open)<br>OR<br>External beam radiotherapy to prostate +/- androgen deprivation therapy +/- external beam radiotherapy to pelvic lymph nodes<br>OR<br>LDR brachytherapy alone (for selected intermediate risk patients) |
| **O – Outcomes**<br>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:*<br>*Biochemical failure (e.g. ASTRO or Phoenix definition)*<br>*Overall survival*<br>*Prostate cancer specific survival*<br>*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*<br>*Quality of life (for example, NEI-VFQ-25)*<br><br>*Important to decision-making:*<br>*Cost effectiveness* |
| **Assumptions / limits applied to search** | |
| **Inclusion Criteria** | Peer reviewed articles published in journals<br>Language – English only<br>Time frame – studies published in the last 10 years (including 2008)<br>Meta-analyses or controlled studies preferable to cohort studies or case series |
| **Exclusion Criteria** | Low risk prostate cancer<br>Definite metastases to lymph nodes or other organs radiologically or on biopsy<br>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: 233
- Total number of publications considered potentially relevant: 53
- Total number of publications selected for inclusion in this briefing: 7

| 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. 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* 2015, 33:7_suppl,3-3 | Excluded.<br>Conference abstract. ASCENDE-RT does not include any patients treated with HDRPB so out of scope for this RER. |
| 2 | Hoskin, P., Rojas, A., Bownes, P., Lowe, G., Ostler, P. and Bryant, L. Randomised trial of external beam radiotherapy | Included. |

| | | |
|---|---|---|
| | alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. *Radiotherapy and Oncology* 2012, 103(2): 217-222. | |
| 3 | Chin J., Rumble R.B., Kollmeier M., Heath E., Efstathiou J., Dorff T., Berman B., Feifer A., Jacques A & Loblaw D.A. Brachytherapy for Patients With Prostate Cancer: American Society of Clinical Oncology/Cancer Care Ontario Joint Guideline Update. *Journal of Clinical Oncology* 2017, 35(15): 1737-1745 | Excluded.<br>No pooling of results.<br>Only 2 of the included studies are RCTs of HDR boost; Hoskin already included separately; Sathya out of scope because published before 2008 |

## 12 References


Cancer Research UK, 2019. Prostate cancer statistics https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer?_ga=2.109561797.1300704633.1546942372-2000096307.1546942372 accessed 2/1/2019

Carter HB, 2011. Management of low (favourable)-risk prostate cancer. *BJU International* 108(11): 1684-1695.

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