Clinical Commissioning Policy: Brachytherapy dose escalation with external beam radiotherapy for intermediate- and high-risk localised prostate cancer (adults) (210502P) [URN 1831]

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Commissioning position

Summary

Brachytherapy dose escalation with external beam radiotherapy for intermediate- and high-risk localised prostate cancer is recommended as a routine commissioning treatment option within the criteria set out in this document.

The policy is restricted to certain age groups as there is insufficient evidence to confirm safety and it is not recommended to be used in those age groups not included in the policy.

Executive summary

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Plain language summary

About prostate cancer

The prostate is a small gland located at the base of the bladder. Prostate cancer only affects people with a prostate; this means that this policy applies to any person with a prostate. Prostate cancer usually develops very slowly, meaning that there may be no signs of the cancer for many years. It is the most common cancer affecting men in the UK, with 41,736 new cases in 2011 (Cancer Research UK, 2017).

When prostate cancer is diagnosed it is 'staged'; this provides an indication of how large the cancer is as well as how far it has spread. This helps to identify the best treatment for patients. Localised prostate cancer is when the cancer is contained within the prostate and has not spread anywhere else in the body. As well as being staged, localised prostate cancer is also risk assessed into three groups (low-, intermediate- and high-risk) depending on how likely the cancer is to spread or return. This policy is specifically for people with intermediate- or high-risk localised prostate cancer.

About current treatments

There are many treatment options for intermediate- or high-risk localised prostate cancer including active surveillance, hormone therapy, surgery and radiotherapy.

For people having radical (i.e. curative) radiotherapy for localised prostate cancer, the standard of care in England is to use hypofractionated external beam radiotherapy (National Institute for Health and Care Excellence (NICE), 2019). This form of radiotherapy delivers high doses of radiation from outside of the body, using a shorter number of treatments as compared to more conventional radiotherapy treatment regimens.

However, some people are not able to have hypofractionated external beam radiotherapy because of the spread of the cancer. Where hypofractionated external beam radiotherapy is contradicted, treatment with conventional external beam radiotherapy can be offered (NICE, 2019).

About the new treatment

When treating with external beam radiotherapy, some people with intermediate- or high-risk localised prostate cancer may benefit from a higher dose of radiotherapy to the prostate.

Brachytherapy is another form of radiotherapy which involves placing radioactive material directly into a cancer. A brachytherapy boost in combination with external beam radiotherapy enables a higher dose of radiation to be delivered to the prostate. This is known as dose escalation or boost. It is thought that this approach may allow you to spend a longer amount of time after the treatment without signs that your cancer has returned.

Brachytherapy can be given either before or after treatment with external beam radiotherapy. There are two methods of delivering brachytherapy:

- Low-dose rate (LDR) brachytherapy, whereby tiny radioactive seeds are put into the prostate. The seeds stay in the prostate and give a steady dose of radiation over a few months.
- High-dose rate (HDR) brachytherapy, a procedure which involves the insertion of thin tubes into the prostate gland. A source of radiation is then passed down the tubes into the prostate for a few minutes to destroy cancer cells. The source of radiation is then removed, so no radiation is left in the body.

Some centres are now offering brachytherapy for the treatment of intermediate- or high-risk prostate cancer.

What we have decided

NHS England has carefully reviewed the evidence for the treatment of intermediate- and high-risk localised prostate cancer with brachytherapy dose escalation with external beam radiotherapy. We have concluded that there is enough evidence to make the treatment available at this time, alongside other radiotherapy treatment options for localised prostate cancer and in line with the clinical criteria as set out in this document.

Links and updates to other policies

This document links to the following documents:

- NHS England (2017). Clinical commissioning policy: Hypofractionated external beam radiotherapy in the treatment of localised prostate cancer (adults) (NHS England Reference: 170021/P).
- NHS England (2013). Service Specification for Brachytherapy (NHS England Reference: B01/S/b).
- NHS England (2019). Service Specifications for External Beam Radiotherapy Services (Adults). (NHS England Reference: 170091S).

Committee discussion

Clinical Panel considered that the proposition reflected the evidence base and supported it proceeding a routine commissioning policy.

See the committee papers (link) for full details of the evidence.

The condition

Localised prostate cancer is a cancer contained within the prostate gland that has not metastasised, or spread, to other parts of the body. Localised prostate cancer is classified according to the level of risk of the cancer spreading to other parts of the body. The categories are low-, intermediate- and high-risk and are stratified by the stage of disease (size of tumour and extent of spread in the body), prostate specific antigen (PSA) levels and the Gleason score (resemblance of cells to either normal or cancerous tissue; see Table 1).

	Low Risk	Intermediate Risk	High Risk
Stage	T1, T2a	T2b, T2c	≥T3
PSA (ng/ml)	<10ng/ml	10-20ng/ml	>20ng/ml
Gleason grade	≤6	7	≥8-10

Table 1. Stratification of localised prostate cancer into low-, intermediate- and high-risk based on stage, PSA level and grade (NICE NG131, 2019).

Current treatments

Radiotherapy for intermediate- or high-risk localised prostate cancer can be administered either via an external source of radiation from outside of the body (external beam radiotherapy (EBRT)) or by placing a source of radiation directly into the cancer (brachytherapy).

For people having radical radiotherapy for localised prostate cancer the standard of care is hypofractionated EBRT, unless contraindicated (NICE, 2019). The radiation dose for hypofractionated EBRT is 60 Gray (Gy) with treatment typically delivered in 20 fractions of radiotherapy over 27 days. Where hypofractionated EBRT is contraindicated, people with localised prostate cancer may be offered 74Gy in 37 fractions EBRT (NICE, 2019).

When treating with conventional EBRT, some people with intermediate- or high-risk localised prostate cancer require a higher dose of radiotherapy to the prostate to minimise the chances of the cancer returning. However, there are limitations to the amount of radiation that can be delivered to the prostate by EBRT without increasing the risk of damaging nearby structures such as the rectum or bladder.

Combining EBRT with brachytherapy, known as a dose escalation or boost, could reduce the risk of the cancer returning for some people and minimise damage to important nearby structures.

Brachytherapy is performed via a trans-perineal approach with direct trans-rectal ultrasound guidance, whilst under general anaesthesia. There are two techniques of brachytherapy used to treat localised prostate cancer:

- Low-dose rate (LDR) brachytherapy: radioactive seeds are permanently implanted into the prostate via loaded needles to deliver a radiation dose over several months
- High-dose rate (HDR) brachytherapy: a radioactive source delivering a radioactive dose is inserted into the prostate via hollow needles and then removed during the same procedure, resulting in short exposure to high dose radiation.

After treatment, PSA levels are monitored as increasing levels may suggest the cancer has returned or spread to other parts of the body. The period until PSA levels rise is known as

biochemical progression free survival (PFS) and a brachytherapy boost (in combination with EBRT) has been shown to increase this.

The new intervention

The new treatment involves routinely offering dose escalation by combining a brachytherapy boost (either LDR or HDR brachytherapy) with EBRT. NICE recommends the consideration of either LDR or HDR brachytherapy in combination with EBRT for people with intermediate- and high-risk localised prostate cancer (NICE, 2019).

There is high quality evidence that both LDR and HDR brachytherapy with EBRT improve biochemical relapse free survival. Based on clinical opinion, the benefit of prolonging biochemical progression free survival includes people having a longer time-period without having to undergo hormone ablative treatments for recurrent prostate cancer and its associated side effects. However, there is an increased side effect profile associated with LDR and HDR brachytherapy. This must be balanced with the benefits of having the treatment. All patients must be fully informed of all radiotherapy treatment options including the risks and benefits of LDR/HDR to be able to make an informed choice.

Epidemiology and needs assessment

Prostate cancer is the most common cancer in men in the UK, with 41,736 newly diagnosed cases in 2011 (Cancer Research UK, 2017). The net survival for people diagnosed with prostate cancer in 2010-11 in England and Wales was 94% 1-year survival, 84.8% 5-year survival and 83.8% 10-year survival (Cancer Research UK, 2017).

Approximately 60% of all diagnosed cases of prostate cancer are estimated to be localised. Of these, approximately two thirds of cases are estimated to be intermediate- or high-risk (Carter, 2011). This equates to around 22,000 patients with intermediate- or high-risk localised prostate cancer per year in England.

The national Radiotherapy Dataset (RTDS) suggests that approximately 14,700 patients receive radical prostate EBRT every year in England (RTDS, 2017). The Policy Working Group estimate that approximately 25% of these patients could meet the eligibility criteria as set out in the policy and be offered brachytherapy dose escalation. This equates to 3,750 patients per year in England. It is estimated that approximately 900 patients are currently already treated using brachytherapy dose escalation for this indication per year in England.

Evidence summary

NHS England has concluded that there is sufficient evidence to support a policy for the routine commissioning of HDR or LDR brachytherapy dose escalation to be offered as a treatment option for the indication of intermediate- and high-risk localised prostate cancer.

Summary of Evidence: High Dose Rate Brachytherapy Dose Escalation (boost):

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, 2012; 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, 2012; 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).

1. 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 lower in the group receiving HDRPB (88%, 81% and 67%) compared to those receiving EBRT (89%, 88% and 79%) but this was not a statistically significant difference (Hoskin et al, 2012).
- *Overall mortality (OM).* (One study, n=621). There was no statistically significant difference in OM at 10 years between the group receiving HDRPB (12.92%; 42/325) and the group receiving EBRT alone (23.31%; 69/296) (p=0.02) (Wedde et al, 2018).
- *Prostate cancer-specific mortality (PCSM).* (One study, n=621). PCSM at 5 and 10 years was lower (1% and 2.5% respectively) in the group receiving HDRPB compared to the group receiving EBRT alone (3.1% and 8.2% respectively) and this difference was statistically significant (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 higher (75%, 66% and 46%) in the group receiving HDRPB than in those receiving EBRT alone (61%, 48% and 39%) and this difference was statistically significant (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 compared to 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 deaths 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 compared to 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[1]. 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 compared to 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: Hazard Ratio (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

[1] Risk categories did not correspond to those defined by the National Comprehensive Cancer Network or NICE

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)[2].
- *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 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)[3].

2. 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[4] by 5 and 7 years respectively was 26% and 31% in the group receiving HDRPB and 26% and 30% in those receiving EBRT alone but this was not a statistically significant difference (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 but this was not a statistically significant difference (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[5] by 5 and 7 years respectively was 7% and 7% in the group receiving HDRPB and 6% and 6% in those receiving EBRT alone but this was not a statistically significant difference (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 but this was not a statistically significant difference (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 but this was not a statistically significant difference (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).

[2] 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

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

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

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

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[6] 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 quality of life score (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).
- *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[7] 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).

3. 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 Rapid Evidence Review. 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[8] (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

[6] 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.

[7] 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.

[8] Added note by the PWG: the EBRT delivered in this RCT (Hoskin et al 2012) was hypofractionated; equivalent to 64-70 Gy in fractionation.

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).

Summary of Evidence: Low Dose Rate Brachytherapy Dose Escalation (boost):

Six papers were included in this rapid evidence review. Three papers reported findings from the ASCENDE-RT trial which compared external beam radiotherapy and low dose rate prostate brachytherapy boost (LDRPB) with dose-escalated external beam radiotherapy (DE-EBRT) in 398 patients with intermediate and high risk localised prostate cancer (Morris et al 2017; Rodda et al 2017a; Rodda et al 2017b).

In addition, two retrospective studies have been included. These reported longer-term follow-up of outcomes similar to those in ASCENDE-RT for high or intermediate risk prostate cancer patients treated with LDRPB or DE-EBRT (Luo et al 2018; Abugharib et al 2017). A large database analysis of over 25,000 subjects treated with either LDRPB or DE-EBRT and outcomes reported to seven years has also been included (Johnson et al 2017).

1. **Clinical Effectiveness**

- *Overall survival* (three studies, n=398, n=25,038, n=320). In the ASCENDE-RT RCT there was no significant difference in overall survival (OS) in patients randomised to LDRPB compared with DE-EBRT at 5 years (91.3% vs 88.7%), 7 years (85.7% vs 81.5%) and 9yrs (77.9% vs 73.6%) (p=0.293) (Morris et al, 2017). There was a significant benefit in OS at 7 years for patients receiving LDRPB compared with DE-EBRT in the large database study (82% vs 73%, Hazard ratio (HR) 0.70 (95% CI 0.64-0.77)) (Johnson et al 2017). There was a significant OS benefit from 7 years onwards, up to 15 years follow-up, in the retrospective study by Luo et al (2018), with median OS of 12.3 years for LDRPB and 9.1 years for DE-EBRT (HR 6.358, (95% CI 5.733- 6.627), p<0.001).
- *Biochemical progression*[9] (three studies, n=398, n=579, n=320). Two studies reported significantly better biochemical progression-free survival (bPFS) for the LDRPB group, compared with DE-EBRT. In the ASCENDE-RT trial bPFS at 5, 7 and 9 years post-treatment was 88.7% +/- SD 4.8, 86.2% +/- SD 5.4 and 83.3% +/- SD 6.6 for patients randomised to LDRPB compared with 83.8% +/- SD 5.6, 75.0% +/- SD 7.2 and 62.4% +/- SD 9.8 for DE-EBRT (log-rank p<0.001; HR 2.04 (95%CI 1.25-3.33, p=0.004)) (Morris et al 2017). In a study of intermediate-risk patients, Abugharib et al (2017) reported bPFS at 5 and 10 years of 94.1% (95%CI 90.4-97.8) and 91.7% (95%CI 86.8-96.6) for patients receiving LDRPB, compared with 89.2% (95%CI 85.9-92.5) and 75.4% (95%CI 70.1-80.7) for those receiving DE-EBRT (p=0.014).

  On follow-up up to 15 years, median time to biochemical progression was 9.8 years (95%CI 8.5-10.7) for patients receiving LDRPB compared with 6.5 years (95%CI 4.8-8.1) for DE-EBRT, a significant difference (HR: 5.126 (95%CI 4.251-6.306), p < 0.001) (Luo et al 2018).
- *Biochemical failure* (one study, n=398). Morris et al (2017) reported a significantly higher risk of biochemical failure in subjects who were randomised to DE-EBRT compared with those randomised to LDRPB. On multivariable analysis the HR of biochemical failure in

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

those randomised to DE-EBRT vs those randomised to LDRPB was 2.04 (95%CI 1.25-3.33, p=0.004).

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

2. Safety

- *Acute genitourinary (GU) morbidity* (two studies, n=383, n=320). Up to 6 months after treatment, 19.1% of LDRPB patients compared with 40.5% of DE-EBRT patients in ASCENDE-RT were symptom-free (p<0.0001), and 30.0% of LDRPB patients compared with 15.8% of DE-EBRT patients had moderate GU symptoms (p<0.0001) (Rodda et al, 2017a). Luo et al (2018) also found significantly less acute GU morbidity among DE-EBRT patients.
- *Late genitourinary (GU) morbidity* (three studies, n=383, n=320, n=579). Up to 5 years after starting treatment 20.6% LDRPB patients compared with 29.6% DE-EBRT patients in ASCENDE-RT had no late GU symptoms (p=0.003), 32.8% LDRPB patients compared with 20.6% DE-EBRT patients had moderate GU symptoms (p=0.002) and 18.4% LDRPB patients compared with 5.2% DE-EBRT patients had moderately severe (p<0.001) GU symptoms (Rodda et al 2017a). The prevalence of late grade ≥3 (moderately severe or worse) GU adverse events at 2 years was LDRPB 7.0% vs DE-EBRT 1.1% (p=0.005), and at 5 years was LDRPB 8.6% vs DE-EBRT 2.2% (p=0.058). Luo et al (2018) found only one symptom (frequency/nocturia) out of five measured was significantly different between groups in the longer term, being more common among the LDRPB group (LDRPB 25.12% vs DE-EBRT 15.38%, p=0.041). Abugharib et al (2017) found a significant difference in the cumulative incidence of severe GU toxicity at 6 years, (LDRPB 3.6% vs DE-EBRT 1.4%) and 10 years (LDRPB 7.5% vs DE-EBRT 1.4%, p=0.026).
- *Acute gastrointestinal (GI) morbidity* (two studies, n=383, n=320). There was no significant difference between treatment groups in ASCENDE-RT in acute GI morbidity up to 6 months (Rodda et al, 2017a). In the LDRPB vs DE-EBRT groups 46.2% vs 45.1% of patients had no symptoms (p=0.961), 39.3% vs 33.3% had mild symptoms (p=0.271), 9% vs 14.3% had moderate symptoms (p=0.090) and none had worse than moderate symptoms. Luo et al (2018) also found no significant difference between the groups, with 88.67% of LDRPB and 90.6% of DE-EBRT patients having no symptoms (p=0.590).
- *Late gastrointestinal (GI) morbidity* (three studies, n=383, n=320, n=579). There was no significant difference between treatment groups in ASCENDE-RT in late GI morbidity up to 5 years after starting pelvic irradiation (Rodda et al, 2017a). In the LDRPB vs DE-EBRT groups, 31.3% vs 35.8% of patients had no symptoms (p=0.343), 42% vs 48.2%

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

had mild symptoms (p=0.322), 31.3% vs 20.2% had moderate symptoms (p=0.205) and 8.1% vs 3.2% moderately severe symptoms (p=0.124). The prevalence of late grade ≥3 GI adverse events was 1.7% vs 1.1% at 2 years and 1.0% vs 2.2% at 5 years, with no significant differences between groups (p values not reported). Luo et al (2018) found no difference between treatment groups in five GI symptoms at longer term follow-up. Abugharib (2017) found that the cumulative incidence of moderate or worse GI toxicity in the LDRPB vs DE-BERT groups was 31.2% vs 33.1% at 6 years, and 35.5% vs 33.1% at 10 years, with no significant difference between groups (p=0.45).

- *Erectile function* (one study, n=383). Before starting androgen deprivation therapy (ADT) 63.8% men in the LDRPB group and 61% men in the DE-EBRT group reported adequate erectile function. This declined to 5.2% vs 7.1% one year after starting treatment, recovering to 33.9% vs 30.6% after 5 years, with no significant difference between groups (p=0.60).
- *Median time to first skeletal-related event* (one study, n=320). Median time was significantly longer in those receiving LDRPB (10.4 years (95%CI 8.9-12.2)) compared with DE-EBRT (8.2 years (95%CI 7.1-10.5)), HR 3.361 (95%CI 2.925-3.815), p < 0.001 (Luo et al 2018).
- *Median time to initiation of cytotoxic chemotherapy* (one study, n=320). Median time was significantly longer in those receiving LDRPB (11.6 years (95%CI 9.8-12.7)) compared with DE-EBRT (8.8 years (95%CI 6.3-10.9)), HR 1.627 (95%CI 1.311-1.809), p = 0.007 (Luo et al 2018).
- *Changes in health-related quality of life* (HRQoL) (one study, n=357). Using the SF36v2[11], baseline scores were between 80-90 for most domains (physical function, bodily pain, role physical, social function, role emotional, urinary function), between 70-80 for vitality, general health and mental health, >90 for bowel function, and 58-60 for sexual function. At 12 months from baseline there had been a decline in both treatment groups in all domains except mental health. The decline was significantly greater in the LDRPB group compared with the DE-EBRT group for physical health (p=0.04), vitality (p=0.02), role physical (p=0.01), bowel function (p=0.01) and sexual function (p=0.02). For other domains there was no significant difference in score change between treatment groups. The largest decline (LDRPB vs DE-EBRT) was for sexual function (-30.6 vs -23.8), with larger declines also for physical function (-11.6 vs -7.4), role physical (-20.9 vs -13.1), vitality (-12.2 vs -7.4), and bowel function (-12.2 vs -0.1).

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

3. Cost-effectiveness:

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

The ASCENDE-RT trial, reported by Morris et al (2017), Rodda et al (2017a) and Rodda et al (2017b), appears to have been a well-conducted RCT whose findings may be regarded as

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

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

Implementation

LDR or HDR brachytherapy dose escalation with EBRT may be considered as a potential treatment option for appropriate patients based on the criteria outlined below:

- All patients with prostate cancer should have their care managed by a variety of different specialists working together as part of a tumour specific cancer multi-disciplinary team (MDT). All possible treatment options should be assessed (see Appendix 3). The prostate cancer MDT is responsible for radiotherapy case selection and should take into consideration patient comorbidities, potential adverse events and likely outcomes of treatment
- The decision to treat with either LDR or HDR brachytherapy dose escalation will be made jointly between the patient and the clinical oncologist using an approved Shared Decision Making Tool (Appendix 1)
- All patients must be fully informed of all radiotherapy treatment options including the risks and benefits of HDR / LDR to be able to make an informed choice
- Brachytherapy alone should not be offered to people with high-risk localised prostate cancer (NICE, 2019).

Inclusion criteria

LDR or HDR brachytherapy dose escalation in combination with EBRT may be considered in people who:

- Have confirmed intermediate (Gleason 7 plus PSA 10-20) or high-risk localised prostate cancer requiring primary, radical treatment
- Have acceptable urinary function as assessed by the International Prostate Symptom Score of <20 (IPSS)
- Have no evidence of distant metastases
- Have a life expectancy 10 years or more; and
- Are suitable for spinal or general anaesthetic (GA).

Exclusion criteria

LDR or HDR brachytherapy dose escalation in combination with EBRT is unsuitable in people with:

- Confirmed low-risk localised prostate cancer;
- Evidence of metastases;
- Moderate or severe comorbidity;
- Life expectancy of less than 10 years;
- Poor urinary function (defined as IPSS >20);
- Significant rectal pathology e.g. rectal fistula; and
- Unsuitable for spinal/GA or lithotomy position.

Intervention criteria

In choosing between LDR or HDR or EBRT clinicians should balance the benefit of improved biochemical control with the risk of heightened side-effects with the particular treatment modalities. Appendix 2 can be utilised to help optimise patient selection for brachytherapy boost. This should be used in conjunction with the Shared Decision-Making Tool as per Appendix 1.

The recommended dose and fractionation schedule can be found in Table 2 below.

Treatment	Recommended Dose and Fractionation Schedule
External beam radiotherapy with HDR brachytherapy without pelvic node irradiation	37.5 Gy in 15 fractions, over 21 days
External beam radiotherapy with HDR brachytherapy with pelvic node irradiation	46 Gy in 23 fractions, over 28 days
External beam radiotherapy with LDR brachytherapy with/without pelvic node irradiation	46 Gy in 23 fractions, over 28 days

Table 2: Recommended dose and fractionation schedule for brachytherapy in the treatment of intermediate- and high-risk localised prostate cancer

LDR or HDR brachytherapy will be undertaken within 2 to 3 weeks before or after EBRT. This requires general or spinal anaesthesia and an overnight stay in hospital. A dose of 110Gy slow release LDR or 15Gy HDR brachytherapy will be given to the prostate under image guidance.

A high level of treatment accuracy using image guidance (IGRT) at appropriate points during treatment is required and dose constraints must be rigorously applied.

To minimise the heightened risk of grade 3 urinary toxicity for LDR brachytherapy, providers should follow the volume definitions published in the European Society for Radiotherapy & Oncology (ESTRO)/European Association of Urology (EAU)/ The European Organisation for the Research and Treatment of Cancer (EORTC) recommendations (Ash et al, 2000; Hoskin et al, 2013).

Patient pathway

The Service Specification for External Beam Radiotherapy Services (NHS England Reference: 170091S) and the Service Specification for Brachytherapy (NHS England Reference: B01/S/b) describes the detail of the care pathways for this service.

Radiotherapy is part of an overall cancer management and treatment pathway (see Appendix 3). Decisions on the overall treatment plan should relate back to an MDT discussion and decision.

Patients requiring EBRT with either LDR or HDR brachytherapy are referred to a clinical oncologist for assessment, treatment planning and delivery of radiotherapy. Both LDR and HDR brachytherapy are delivered in a single session requiring a general or spinal anaesthetic and trans-rectal ultrasound guided insertion of radioactive seeds (LDR) or hollow needles (HDR) into the prostate via the perineum. Treatment must occur in an environment with suitable radiation protection. Typically, patients will be treated as a day case or require one overnight stay to recover from the procedure.

Governance arrangements

The Service Specification for External Beam Radiotherapy Services (NHS England Reference: 170091S) describes the governance arrangements for this service. It is imperative that the radiotherapy service is compliant with the Ionising Radiation (Medical Exposure) Regulations (IR(ME)R) 2017.

The Service Specification for Brachytherapy (NHS England Reference: B01/S/b) describes the service standards and requirements of providers eligible to deliver this service. Clinical governance systems and policies should be in place and integrated into organisational governance with clear lines of accountability and responsibility for all clinical governance functions. Providers should produce annual clinical governance reports as part of NHS clinical governance reporting systems.

Mechanism for funding

EBRT planning and delivery is reimbursed through national tariff. Brachytherapy is subject to national coding and local pricing agreements through established NHS England funding streams.

Audit requirements

Radiotherapy providers must submit their activity every month to the national RTDS. Radiotherapy services are subject to regular self-assessment by the National Specialised Commissioning Quality Surveillance Team. The quality system and treatment protocols will be subject to regular clinical and management audit.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Definitions

Biochemical progression	Biochemical markers of disease activity, such as PSA, are measured and monitored to indicate progression of cancer.
External beam radiotherapy (EBRT)	A form of radiotherapy delivered by a linear accelerator, which focuses high-energy radiation beams onto the area requiring treatment from outside of the body.
Fractionation	The term used to describe how the full dose of radiation is divided into a number of smaller doses called fractions. The fractions are given as a series of treatment sessions which make up a radiotherapy course.
Gleason score	A grading system which is used to help evaluate the prognosis of people with prostate cancer based on its microscopic appearance. A low score indicates that the cancer is likely to grow at a slow rate whilst a high Gleason score indicates that the cancer is likely to grow more quickly.
Gray (Gy)	The international system (SI) unit of radiation dose. One Gray is the absorption of one joule of energy, in the form of ionizing radiation, per kilogram of matter.
High dose rate (HDR) prostate brachytherapy	Involves the transrectal ultrasound 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 all removed at the completion of the procedure.
High risk localised prostate cancer	Defined as: stage ≥T3; PSA >20ng/ml; and Gleason grade ≥8-10.
Hypofractionation	Describes a treatment regimen that delivers high doses of radiation using a shorter number of treatments as compared to 2Gy treatment regimens.
Intermediate risk localised prostate cancer	Defined as: stage T2b, T2c; PSA 10-20ng/ml; and Gleason grade 7.
International Prostate Symptom Score (IPSS)	A score derived from a quality of life questionnaire which looks to assess the severity of an individual's water work symptoms. A score of 0 to 7 indicates mild symptoms, 8 to 19 indicates moderate symptoms and 20 to 35 indicates severe symptoms.
Localised prostate cancer	Defined as disease which is confined to the prostate gland and immediate surrounding area including the seminal vesicles. Localised prostate cancer is grouped into low-, intermediate- and high-risk categories. The risk category influences how the prostate cancer is managed. This assessment is based on tumour extent ("T" stage), histological architecture (Gleason score) and PSA level.
Low dose rate (LDR) prostate brachytherapy	Involves transrectal ultrasound guided insertion of permanent iodine 125 seeds which release radiation over the following months into the prostate. Typically delivered at a single session.
Low risk localised prostate cancer	Defined as: stage T1, T2a; PSA <10ng/ml; and Gleason grade ≤6.
Prostate	A walnut sized gland in the pelvis which is located underneath the bladder and surrounds the urethra. The main function of the prostate is to produce a thick white fluid that is mixed with the sperm produced by the testicles, to create semen.

Prostate brachytherapy	Involves the insertion of needles via the perineum into the prostate under transrectal ultrasound guidance for the delivery of radiotherapy directly into the tumour.
Prostate specific antigen (PSA)	A protein released by the prostate and prostate cancer cells which may indicate a diagnosis of prostate cancer or relapse following prostate cancer treatment.
Pubic arch interference	The pubic arch, located on the pelvic floor, sometimes prevents needle insertion to the prostate, known as pubic arch interference. Presence of this overlap interrupts accurate seed placement.
Radiotherapy	The safe use of ionising radiation to kill cancer cells with the aim of cure or effective palliation.
Risk	Localised prostate cancer is grouped into low-, intermediate- and high-risk categories. The risk category influences how the prostate cancer is managed. This assessment is based on tumour extent (“T” stage), histological architecture (Gleason score) and prostate specific antigen level.
Stage/staging	Staging is a way of describing the size of a cancer and how far it has grown.
Target volume	Clinical Target Volume (CTV) is a tissue volume that contains the Gross Tumour and/or subclinical malignant disease at a certain probability level. This volume thus has to be treated adequately to achieve cure. The planning target volume (PTV), allows for uncertainties in planning or treatment delivery. It is a geometric concept designed to ensure that the radiotherapy dose is actually delivered to the CTV.
Transrectal Ultrasound (TRUS)	Imaging of the prostate gland and periprostatic tissues with an ultrasound transducer inserted into the anus and directed toward the anterior rectum.
Transurethral resection of the prostate (TURP)	A surgical procedure that involves cutting away a section of the prostate. It is used to treat symptoms of an enlarged prostate which may be slowing down or stopping urine flow.
Tumour, Node, Metastases (TNM) staging system	An international cancer staging system which describes the size of the initial cancer (the primary tumour), whether the cancer has spread to the lymph nodes, and whether it has spread to a different part of the body (metastasised).

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Appendix 1: Decision aid – Radiotherapy options for localised prostate Cancer (intermediate/high risk)

You and your doctor have agreed that radiotherapy is the best option to treat your prostate cancer.

How does radiotherapy work?

Radiotherapy can be given to you in different doses. Usually, the higher the dose, the more likely it is to kill the cancer cells in your prostate. However, a higher dose is also more likely to damage nearby non cancer, healthy cells. Cells in your bowel, bladder and sex organs are commonly affected. This can cause problems such as diarrhoea, difficulty passing water and problems getting an erection. Your doctor and other health professionals involved in your care have to balance giving as much radiotherapy to the cancer cells as possible whilst reducing the chances of damaging nearby healthy cells so side effects are reduced.

External beam radiotherapy (EBRT)

The standard way of giving radiotherapy for prostate cancer is called external beam radiotherapy (EBRT). Machines called linear accelerators target X-ray beams from outside the body at the cancer cells in the prostate. EBRT can be given in different doses (also called schedules). In the UK, the most common schedule gives a total dose of 60 Gray (how much radiation you need) in 20 fractions. This means you will have to visit your radiotherapy centre every day for 4 weeks to receive the total dose (60 Gray over 20 visits).

Brachytherapy

As well as external beam radiotherapy alone, there is also the choice of combining a lower dose of EBRT with another form of radiotherapy to give a higher radiation dose directly to the prostate. This will help kill the cancer cells. This can help reduce the chances of your cancer returning. This is called **BRACHYTHERAPY**. Radioactive material is placed directly into your prostate using radioactive seeds **(low dose permanent brachytherapy)** or via hollow needles placed for a short time into your prostate **(high dose temporary brachytherapy)**. This is usually done as a day case for permanent implants and needs an overnight stay for temporary implants. Both procedures are carried out under a general or spinal anaesthetic. LDR or HDR brachytherapy will be undertaken within 2 to 3 weeks before or after EBRT.

NICE (national organisation which publishes clinical guidelines) recommends that brachytherapy can be **considered** as an option in patients who have their disease staged as intermediate or high risk localised prostate cancer.

What are the benefits and harms of brachytherapy?

The aim of adding low dose or high dose brachytherapy to external beam radiotherapy is to use higher doses of radiotherapy to damage and kill the cancer cells. The evidence suggests that treating the prostate with higher doses (adding brachytherapy) of radiation will reduce the chances of your cancer coming back. However, at this time we do not know if this means that you will also live longer. This is because the research trials looking at how good brachytherapy is to treat prostate cancer have not been running long enough.

There are possible additional harms with giving this type (brachytherapy boost) of radiation compared with just having external beam radiotherapy alone as the total radiation dose is higher. You are more likely to have side effects such as problems with your waterworks (bladder function) and bowels.

At this time, there is no clear evidence to recommend low dose or high dose brachytherapy over one another in treating your prostate cancer. Both treatments are considered to be equally effective at reducing the chances of your cancer returning. However, low dose brachytherapy is more likely to lead to you having problems with your waterworks.

What does this mean for you?

You will need to think about what matters to you and weigh up the benefits and harms of this radiation boost (low dose or high dose brachytherapy). Other factors that may affect your choice include how often you can travel to hospital, whether you are willing to travel to a hospital further away than your local hospital to receive the treatment (your local hospital may not have the expertise to offer either one or both forms of brachytherapy) and whether you would want to have a general or spinal anaesthetic which would be required for the procedure.

This decision aid is to help you to make up your mind on what radiotherapy option is best for you. When making this decision you should use this tool with your doctor and other health professionals who will explain anything you do not understand and help you to weigh up the choices based on what matters to you.

Different people will feel that some of these things are more important to them than others, so it is important that you make a decision that is right for you. It will also be guided by what you would like to be able to do (for example, at home, at work or with family) over the next few years and this also differs between people.

You may want to discuss this with friends, family or anyone else who you feel can help you to make the right decision for you. If you wanted, they can also join you when you have the discussion with your doctor.

What are my options?

	External beam radiotherapy (EBRT)	EBRT + low dose brachytherapy (LDR)	EBRT + high dose brachytherapy (HDR)
What does it involve?	You will have to visit your radiotherapy centre **20 times** over **four weeks (Monday to Friday)** to receive the total dose of radiotherapy. This dose may not suit some patients (your doctor will discuss this with you). If this is the case, a schedule of 74 Gray (total dose) in 37 daily visits will be given. This means you will have to visit your radiotherapy centre every day for seven and a half weeks (Monday to Friday) to receive the total dose (74 Gray). There is no general anaesthetic or day case procedure involved.	You will have to visit your radiotherapy centre **23 times** over **four and a half weeks (Monday to Friday)** to receive the total dose of radiotherapy. As well as this, you will receive a 'boost' of radiotherapy to decrease the risk of your cancer recurring in the form of **low dose brachytherapy**. This involves either one or two day case procedures under **general anaesthetic or spinal anaesthetic**. You do not normally need to stay overnight. The doctor will perform an ultrasound scan and then place radioactive seeds directly into your prostate using needles and the ultrasound scan. There are however added risks which are discussed below.	You will have to visit your radiotherapy centre **15 or 23 times** over **three weeks or four and a half weeks (Monday to Friday)** to receive the total dose of radiotherapy. As well as this, you will receive a 'boost' of radiotherapy to decrease the risk of your cancer recurring in the form of **high dose brachytherapy**. This involves one overnight stay and the procedure is delivered under **general anaesthetic or spinal anaesthetic**. It involves inserting thin tubes into the prostate gland. A source of radiation is then passed down the tubes into the prostate for a few minutes to destroy cancer cells. The source of radiation is then removed in the same sitting. A catheter placed during the procedure in your bladder to drain urine is usually removed the following day hence the need to stay over-night.

Decision aid

The table below gives you an idea of the benefits and harms with having each of the two types of brachytherapy boost compared with having external beam radiotherapy alone.

There is no study directly comparing low dose brachytherapy boost with high dose brachytherapy boost but specialists believe the benefits are very similar.

Direct comparisons are difficult because separate studies have been done comparing EBRT plus low dose brachytherapy boost with EBRT alone and EBRT plus high dose brachytherapy boost with EBRT alone. These studies measured and reported the treatment effects in slightly different ways and over different time periods.

	EBRT + low dose brachytherapy (LDR)	EBRT + high dose brachytherapy (HDR)
What are the benefits? (The results in each column should not be directly compared with each other.)	The benefits of having EBRT plus low dose brachytherapy **or** EBRT plus high dose brachytherapy over EBRT alone are that you are likely to spend a longer amount of time after the treatment without signs that your cancer has returned.	
	A study has compared EBRT plus low dose brachytherapy boost with EBRT alone. *After 9 years patients were examined to see if their cancer had returned using a blood test called PSA:* *Out of 100 patients treated with EBRT plus low dose brachytherapy compared with 100 treated with EBRT alone:* • *9 years after treatment, **21 more** patients who had EBRT plus low dose brachytherapy boost had no signs that their cancer had returned compared to patients who had EBRT alone.*	*A different study has compared EBRT plus high dose brachytherapy boost with EBRT alone.* *After 7 years patients were examined to see if their cancer had returned using a blood test called PSA:* *Out of 100 patients treated with EBRT plus high dose brachytherapy compared with 100 treated with EBRT alone:* • *7 years after treatment, **18 more** patients treated who had EBRT plus high dose brachytherapy boost had no signs that their cancer had returned compared to patients who had EBRT alone.*

<table>
<tr><td></td><td>EBRT + low dose brachytherapy (LDR)</td><td>EBRT + high dose brachytherapy (HDR)</td></tr>
<tr><td>What are the harms?

(The results in each column should not be directly compared with each other.)</td><td colspan="2">The harms associated with having EBRT plus low dose brachytherapy or EBRT plus high dose brachytherapy over EBRT alone include:
Urinary symptoms - examples of these include feeling the need to pass water more often, urinary incontinence and sometimes needing a catheter (a tube in to the bladder to help you pass water)
Bowel symptoms – increased frequency of stools, runny stools and passing blood from your bottom
Erectile dysfunction.
These side effects are common and can occur if you have any of the treatment options. You are more likely to get problems with your waterworks if you have EBRT plus low dose brachytherapy boost than if you have just EBRT or EBRT plus high dose brachytherapy boost.</td></tr>
<tr><td></td><td>The study comparing EBRT plus low dose brachytherapy boost with EBRT alone also looked at harms.

This study showed that there were more differences in urinary and gastrointestinal side-effects between EBRT plus low dose brachytherapy boost compared with EBRT alone than with EBRT plus high dose brachytherapy boost compared with EBRT alone.

Out of 100 patients treated with EBRT plus low dose brachytherapy compared with 100 treated with EBRT alone:

Within the first 6 months after treatment:
14 more patients who had EBRT and LDR developed moderate urinary symptoms compared to patients who had EBRT alone
2 more patients who had EBRT and LDR developed severe urinary symptoms compared to patients who had EBRT alone
5 fewer patients who had EBRT and LDR developed moderate gastrointestinal symptoms compared to EBRT alone
There was no difference in the number of patients who had severe gastrointestinal symptoms.</td><td>The study comparing EBRT plus high dose brachytherapy boost with EBRT alone also looked at harms.

This study showed that there were less differences in urinary and gastrointestinal side-effects between EBRT plus high dose brachytherapy boost compared with EBRT alone than with EBRT plus low dose brachytherapy boost compared with EBRT alone.

Out of 100 patients treated with EBRT plus high dose brachytherapy compared with 100 treated with EBRT alone:

There was no difference in the number of patients developing severe urinary symptoms at some point in the first 7 years after treatment. Most of these were temporary
However, 8 patients treated with EBRT and HDR developed scarring in the urinary passage requiring surgery compared to 2 treated with EBRT alone
There was no difference in the number of patients developing severe gastrointestinal symptoms at some point in the first 7 years. Most of these were temporary.</td></tr>
</table>

	Between 6 months and 5 years after treatment: • **12 more** patients who had EBRT and LDR developed **moderate urinary symptoms** compared to patients who had EBRT alone • **13 more** patients who had EBRT and LDR developed **severe urinary symptoms** compared to patients who had EBRT alone • **11 more** patients who had EBRT and LDR had **moderate gastrointestinal symptoms** compared to patients who had EBRT alone • **5 more** patients who had EBRT and LDR had **severe gastrointestinal symptoms** of whom **1 required major surgery** compared to patients who had EBRT alone • Overall, **14 more** patients who had EBRT and LDR **required surgery for scarring of their urinary passage** compared to patients who had EBRT alone.	
Other considerations	**Brachytherapy** is given in specialist centres around the country. Not all centres close to you will provide a service of high dose brachytherapy or low dose brachytherapy. This means **you may have to travel much further than your local hospital to receive the treatment.** These options also normally require a general or spinal anaesthetic to put you to sleep during the procedure. This may mean that brachytherapy is not the right treatment for you depending on any other medical conditions you may have (as these may increase the overall risk of the procedure) or your personal wishes based on what is important to you. Your doctor will discuss the risk of general anaesthesia with you.	

All numbers in the table above are **averages**: some people will be at greater or lower risk. **It is not possible to know in advance what will happen to any individual person.**

In summary

If you decide that brachytherapy is the right treatment for you there is no clear evidence to recommend low dose or high dose brachytherapy over one another. These treatments are thought to have similar overall benefits. The decision will depend on whether you are willing to accept the extra risks of the treatment (low or high dose), as well as other factors such as travel time to a specialist centre compared with the possible benefits.

When making this decision you should use this tool with your doctor and other health professionals who will explain anything you do not understand and help you to weigh up the choices based on what matters to you.

Different people will feel that some of these things are more important to them than others, so it is important that you make a decision that is right for you. It will also be guided by what you would like to be able to do in future (for example, at home, at work or with family) over the next few years and this also differs between people.

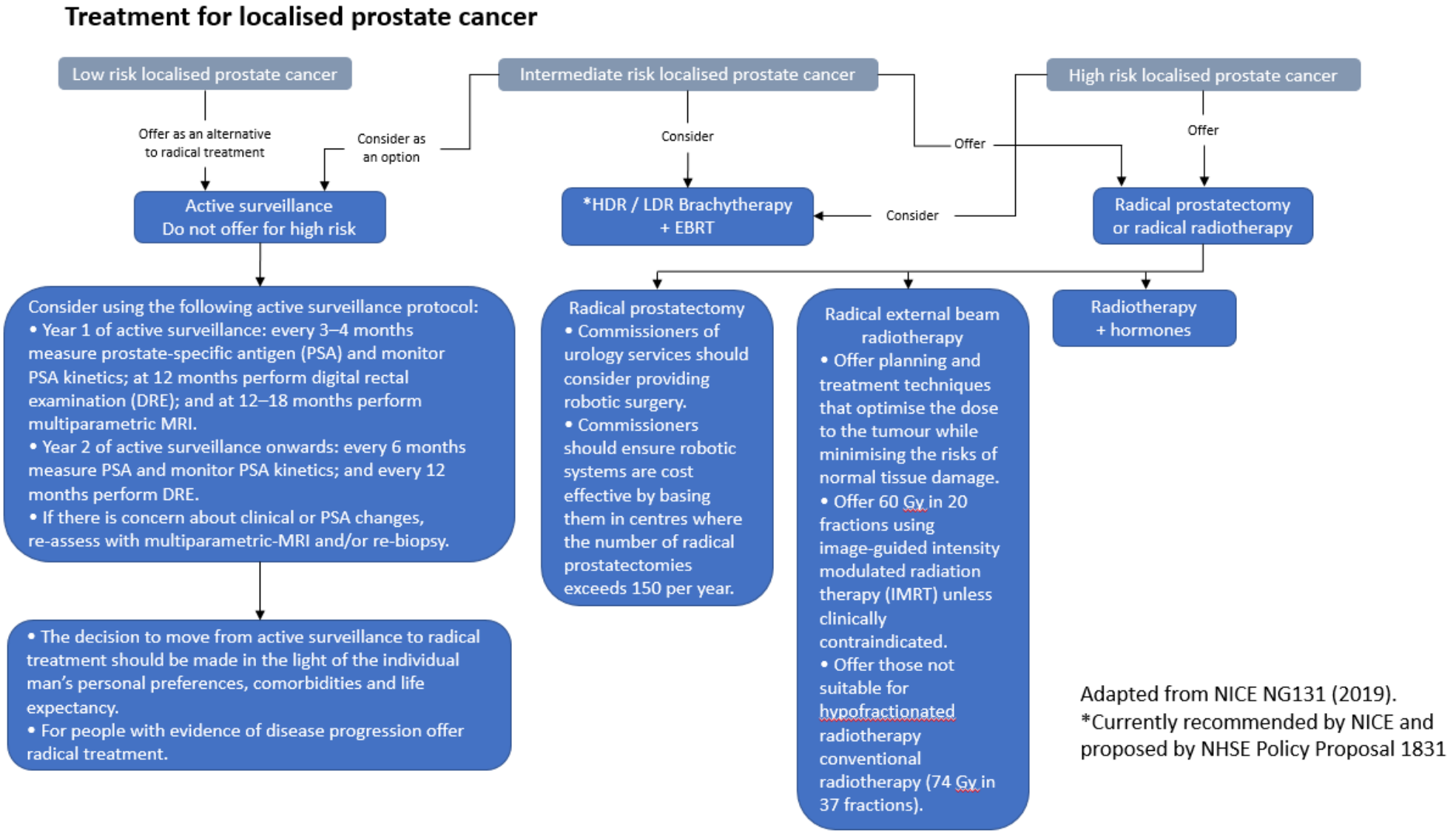
You may want to discuss this with friends, family or anyone else who you feel can help you to make the right decision for you. If you wanted, they can also join you when you have the discussion with your doctor.

Appendix 2: Patient selection

The following table, adapted from the Groupe Européen de Curiethérapie (GEC) and the European Society for Radiotherapy & Oncology (ESTRO) guidelines, 2014, helps to define the risk of heightened side effects as low, moderate or high based on clinical parameters such as prostate volume and level of obstructive symptoms. Patients at high risk of developing side effects based on their clinical parameters should be advised against a particular treatment. Patients at moderate risk may choose a treatment option with a higher risk of side-effects.

	LDR Boost	HDR boost	EBRT alone
Minimal obstructive urinary symptoms (International Prostate Symptom Score [IPSS] <15)	Low	Low	Low
Moderate obstructive symptoms (International Prostate Symptom Score [IPSS] 15-20)	Moderate	Low	Low
Severe obstructive symptoms (International Prostate Symptom Score [IPSS] >20)	High (contra-indicated)	High (contra-indicated)	Moderate
Prostate volume* <50cc	Low	Low	Low
Prostate volume* 50-60cc	Moderate	Low	Low
Prostate volume* 60-80cc	High	Low	Low
Prostate volume* >80cc	High	Low	Moderate
Transurethral resection of the prostate (TURP) < 6 months	High	High	Low/moderate
TURP > 6 months	Moderate	Moderate	Low/
Moderate pubic arch interference	Moderate	Low	Low
Severe pubic arch interference	High	Moderate	Low
Tumour infiltration of bladder neck	High (contra-indicated)	High (contra-indicated)	Moderate

Appendix 3: Localised Prostate Cancer patient pathway



Adapted from NICE NG131 (2019).
*Currently recommended by NICE and proposed by NHSE Policy Proposal 1831