NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of high dose rate brachytherapy for prostate cancer

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in November 2005

Procedure name

- High dose rate (HDR) brachytherapy for prostate cancer
- Interstitial irradiation for prostate cancer

Specialty societies

- British Association of Urological Surgeons
- Royal College of Radiologists
- Institute of Physics and Engineering in Medicine

Description

Indications

Prostate cancer is one of the most common cancers in men. It tends to affect older men, with the risk rising with age. It is not a single disease entity but may be found by biopsy finding or at presentation as metastatic prostate cancer, which may or may not cause any symptoms or shorten life.

Symptoms when they occur include lower urinary tract symptoms suggestive of bladder outflow obstruction, symptoms suggestive of metastases, such as bone pain, or symptoms of a generalised illness such as malaise and weight loss.

Current treatment and alternatives

Prognosis with prostate cancer is variable and depends on the grade of the tumour and stage of the disease. The American Cancer Society estimate that 98% of men

survive at least 5 years, 84% survive at least 10 years, and 56% survive at least 15 years. Comparative figures from Cancer Research UK estimate survival to be 80%, 61%, and 49% at these times respectively. Treatment options depend on the stage of the cancer. Current treatments for localised prostate cancer include watchful waiting, radiotherapy, and radical prostatectomy. Other less invasive interventions are Low dose rate brachytherapy, Cryotherapy, and high intensity focused ultrasound. Metastatic prostate cancer is usually treated with hormone therapy.

What the procedure involves

Brachytherapy is a form of radiotherapy in which delivery of radiation is targeted directly to the prostate gland through a radiation source temporarily implanted within the prostate, as opposed to an external source.

High dose rate brachytherapy differs from low dose rate brachytherapy in that a more active source of radiation is introduced into the prostate temporarily, as opposed to inserting a less active source (permanent seeds) for a longer period.

In high dose rate brachytherapy thin plastic hollow tubes are inserted through a template, through the perineal skin, and into the prostate gland. They enter the skin behind the scrotum and in front of the anus. A radioactive source is then inserted into each tube. A computer controls how long a seed remains in each of the tube, and therefore the amount of radiation can be more effectively targeted. The purpose of this is so that the tumour can be given a higher dose and the urethra and rectum a lower dose.

The tubes are then pulled out, leaving no radioactive material in the prostate gland.

Efficacy

In a controlled trial, overall 5-year actuarial survival with HDR brachytherapy plus external beam radiation therapy (EBRT) was found to be greater than with EBRT alone (86% and 54% respectively; $p < 0.001$)[1]. Across a number of case series this same outcome was estimated to be 85%[2], 89%[3], and 93%[4]. At 10 years, survival was calculated to be 65%[2]. In another series 84% (42/50) of patients survived to 7.2 years' follow-up[5].

Five-year actuarial biochemical control (using prostate-specific antigen [PSA] measures) has been shown to be more common with HDR brachytherapy plus EBRT than with EBRT alone (67% vs 44%; $p < 0.001$)[1], and 3-year biochemical control with HDR or low dose rate brachytherapy to be similar at 98% and 97% respectively[6]. In case series overall actuarial 5-year biochemical control was found to be 77%[2] and 82%[3], and 4-year control to be 75%[7]. One series found that only 5% (2/42) of survivors to 7.2 years had a PSA level > 1 ng/ml[5], and in another series mean PSA fell from 10 to 1.1 ng/ml, and 85% (170/200) of patients achieved PSA nadir < 1 ng/ml over 30 months of follow-up[8]. Where cases were analysed separately based on baseline risk factors using Gleason score, PSA level and cancer stage, actuarial 5-year biochemical control was shown to be significantly less frequent in high-risk cases ($p < 0.0001$[3] and $p < 0.001$)[2].

In a case series that reported outcomes of prostate biopsy findings there was no evidence of viable cancer in 86% (36/42) of cases; however, the accuracy of this outcome may be limited by the sensitivity of the biopsy technique employed[5].

Safety

The definitions used to measure the outcome of potency following HDR brachytherapy varied across the studies included. In men who were potent at baseline, impotency occurred in 14% at 5 years[3], 30% at 30 months[8], 45% at 3 years[6], and 76% (31/41) at 7 years[5].

Where it was reported separately from other urological complications, urethral stricture following HDR brachytherapy was reported in 1.5% (3/200)[8], 4% (6/161)[1], 7% (17/230)[4] and 8%[6].

One case series found acute urinary incontinence in 11% of patients, and there was chronic incontinence in 5% of cases at 3 years follow-up[6]. Another series recorded grade 2 to 3 incontinence in 3% (7/20) of cases[4], and in a third series this occurred in less than 1% (1/200) of cases[8].

In one case series that reported on urinary retention-free survival, this was estimated to have been achieved in 86% of cases at 5 years[9].

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to high dose rate brachytherapy for prostate cancer. Searches were conducted via the following databases, covering the period from their commencement to 21/03/2005: Medline, PreMedline, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches. (See Appendix C for details of search strategy.)

The following selection criteria (Table 1) were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good-quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Patients with prostate cancer
Intervention/test	High dose rate brachytherapy
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on two non randomised controlled studies and six case series (seven reports)

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (Table 2) have been listed in Appendix A.

Existing reviews on this procedure

There were no published reviews identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B details the recommendations made in the guidance listed below.

Interventional procedure

Low dose rate brachytherapy for prostate cancer
http://www.nice.org.uk/ipcat.aspx?c=104838

Clinical guidelines

Prostate Cancer: diagnosis and treatment – Due Nov 2007

Table 2 Summary of key efficacy and safety findings on high dose rate brachytherapy for prostate cancer

Abbreviations used: RP, radical prostatectomy; EBRT/XRT, external beam radiation; CRT, conformal radiotherapy; bRFS, biochemical relapse free survival; bDFS, biochemical disease free survival; QOL, quality of life; LDR, low dose rate brachytherapy; BED, biologically effective dose.

Study details	Key efficacy findings	Key safety findings	Comments
Kestin LL (2000)[1] Non-randomised controlled trial (Matched pair analysis) USA n = 322 (161 HDR brachytherapy) November 1991 to May 1998 161 HDR cases matched by random number generation to a sample of 1109 EBRT-only cases, based on similar PSA level, Gleason score, clinical T stage, and duration of PSA follow-up. All patients had stage I to III adenocarcinoma of the prostate. HDR with US-guided transperineal interstitial radiation by ^{192}Ir at 5.5 to 6.5 Gy for three implant sessions, or 8.25 to 10.5 Gy for two sessions. Following EBRT with a median dose of 46.0 Gy in 1.8 to 2.0 Gy fractions. No patient in either group had hormone therapy unless local or distant failure occurred, or PSA demonstrated biochemical failure. Age = 71 years, baseline PSA = 9.9 ng/ml, T1 = 11%, T2 = 75%, T3 = 13% Follow-up = 3 years. Disclosure of interest: not stated.	**Biochemical failure** Three consecutive rises in PSA after reaching nadir constituted failure (2.5-year FU). Patients in the HDR group had a lower mean PSA nadir (0.4 vs 1.1 ng/ml) (p = 0.009) and reached nadir later (1.5 vs 1.0 years) (p < 0.001) than with EBRT alone. Multivariate analysis showed that higher baseline PSA, Gleason score, T stage and EBRT monotherapy were significantly associated with biomechanical failure (all $p \leq 0.001$). A lower BED was significantly associated with biochemical failure (p < 0.001). **Survival** 5-year actuarial survival End point / HDR / EBRT alone / p = Biochemical control: 67& / 44% / < 0.001 Local failure: 14% / 15% / 0.71 Distant metastasis: 16% / 16% / 0.52 Any clinical failure: 22% / 24% / 0.59 Disease-specific survival: 61% / 25% / < 0.001 Overall survival: 86% / 54% / < 0.001 Cause-specific survival: 95% / 92% / 0.33 In the HDR group 12% (19/161) had clinical failure at a median 1.6 years after treatment, whereas 16% (25/161) of EBRT-only patients had clinical failure.	**Complications** Grade 3 acute toxicity was experienced in 5% (8/161). No patients had grade 4 or 5 toxicity. 4% (6/161) of cases developed urethral stricture. 29% (47/161) developed impotence. The 5-year actuarial rate of grade 3 late complications was 9%.	Patients receiving HDR brachytherapy in this study are also included in Galalae (2004). Matches are drawn from an historical cohort. Variation in the number of HDR sessions given within the active arm. The patients who received a biologically effective dose < 85 Gy had a lower biochemical control rate (52%) than those who received > 85 Gy (88%). Patients in the HDR group were significantly younger than those receiving EBRT alone (p < 0.001). Method of case accrual not stated. Despite the matching criteria there may have been clinical differences between groups that were not adequately accounted for in analysis. The EBRT monotherapy received radiation therapy to the prostate only, while the HDR group received whole pelvic radiation therapy.

Abbreviations used: RP, radical prostatectomy; EBRT/XRT, external beam radiation; CRT, conformal radiotherapy; bRFS, biochemical relapse free survival; bDFS, biochemical disease free survival; QOL, quality of life; LDR, low dose rate brachytherapy; BED, biologically effective dose.

Study details	Key efficacy findings	Key safety findings	Comments
Grills IS (2004)[6] Non-randomised controlled study USA n = 149 (65 HDR brachytherapy) Consecutive cases from 1999 to 2001.with clinically localised prostate cancer stage II and Gleason score < &, and PSA < 10 ng/ml. HDR in 4 fractions twice a day for two days, 9.5 Gy each fraction and a total of 38 Gy. Age = 70 years, prostate volume = 41 cc, stage T1c = 69%, T2a = 30%, T2b = 1%, androgen deprivation = 36%. No EBRT in either group. Follow-up = 35 months (median). Disclosure of interest: not stated.	**Biochemical failure** Three consecutive rises in PSA after reaching nadir constituted failure. Three-year biochemical control was 98% in the HDR group and 97% in the LDR group	**Acute toxicity** Assessed using the common toxicity criteria scale HDR / LDR / p value Dysuria 36% / 67% / < 0.001 Urinary incontinence 11% / 7% / 0.437 Urinary retention 34% / 32% / 0.826 Urinary urgency 54% / 92% / < 0.001 Haematuria 2% / 1% / 0.855 Diarrhoea 14% / 16% / 0.781 Rectal bleeding 6% / 20% / 0.017 Rectal pain 2% / 2% / 0.717 **Chronic toxicity** HDR / LDR / p value Dysuria 15% / 22% / 0.312 Urinary incontinence 5% / 12% / 0.177 Urinary retention 20% / 30% / 0.204 Urinary urgency 32% / 56% / 0.004 Haematuria 13% / 6% / 0.168 Urethral stricture 8% / 3% / 0.177 Diarrhoea 5% / 6% / 0.725 Rectal bleeding 5% / 5% / 0.973 Rectal pain 8% / 5% / 0.450 Cumulative proportion of grade 1 genitourinary toxicity demonstrated that there was more toxicity in the LDR group (p = 0.026). **Potency** Based on the 67 patients whose potency was recorded at baseline, the 3-year actuarial rate of impotence was 45% in the HDR cases and 16% in the LDR cases.	Allocation to treatment group was by patient preference. Outcomes were also reported for both groups without hormone therapy. Toxicity outcomes were assessed by patient questionnaire with an independent observer determining the score. Groups were balanced at baseline in terms of age, clinical stage, PSA level, Gleason score, hormone treatment, genitourinary symptoms, and prostate size. Absolute figures for safety outcomes were not provided. Safety outcomes were analysed by events, not cases.

Abbreviations used: RP, radical prostatectomy; EBRT/XRT, external beam radiation; CRT, conformal radiotherapy; bRFS, biochemical relapse free survival; bDFS, biochemical disease free survival; QOL, quality of life; LDR, low dose rate brachytherapy; BED, biologically effective dose.

Study details	Key efficacy findings	Key safety findings	Comments
Galalae RM (2004)[2] Case series International multicentre n = 611 1986 to 2000 Clinically staged, localised prostate cancer Age = < 65 = 25%, 65 to 75 = 62%, >75 = 13%, Stage T1 = 17%, T2a-b = 45%, T2c = 20%, T3 = 18% EBRT given in 1.8 to 2 Gy fractions 5 times a week to a total of 45.6 to 50 Gy. HDR brachytherapy schedules varied between and within participating institutions to a total BED of 79.6 to 123 Gy. 177 patients received androgen deprivation therapy Follow-up = 5 years Disclosure of interest: not stated	**Survival** Actuarial survival 5 year / 10 year Biochemical control 77% / 73% Overall survival 85% / 65% Cause-specific survival 96% / 92% There was no statistically significant difference in survival between institutions, or with androgen deprivation therapy or not . Actuarial 5-year survival, by baseline risk group based on prognostic factors of Gleason score, PSA level, and stage Outcome / Total / Low / Medium / High Overall survival 85% / 88% / 86% / 85% Cause-specific 96% / 100% / 99% / 95% Biochemical control 77% / 96% / 88% / 69% Disease free 67% / 83% / 75% / 31% Local recurrence 7.4% / 0% / 3.5% / 10% Biochemical control rate was significantly worse in the high-risk group ($p < 0.001$) Multivariate analysis found cancer stage, baseline PSA, and Gleason score to be independent predictors of biochemical control at 5 years (all $p < 0.001$).	No safety outcomes are reported.	A wide clinical range of cases in the cohort. No details of independent outcome assessment. All survival outcomes analysed by Kaplan Meier actuarial survival and absolute figures not presented. Patients were selected for hormone therapy, not randomised to this treatment, with a possibility of selection bias.

Abbreviations used: RP, radical prostatectomy; EBRT/XRT, external beam radiation; CRT, conformal radiotherapy; bRFS, biochemical relapse free survival; bDFS, biochemical disease free survival; QOL, quality of life; LDR, low dose rate brachytherapy; BED, biologically effective dose.

Study details	Key efficacy findings	Key safety findings	Comments
Astrom L (2005)[3] Case series Sweden n = 214 1988 to 2000 EBRT in 2 Gy fractions with total 50 Gy, HDR brachytherapy with US guidance in two 10 Gy fractions (between EBRT periods) Preradiation endocrine therapy given to 70% of cases Age = 64 years, PSA = 9.6 ng/ml, Stage T1 = 21%, T2 = 64%, T3 = 15% Follow-up = 48 months	**Survival** Actuarial 5-year survival, by baseline risk group based on prognostic factors of Gleason score, PSA level, and stage Outcome / Total / Low / Medium / High Biochemical negative: 82% / 92% / 87% / 56% Clinical failure free: 91% / 94% / 93% / 91% Disease specific: 97% / 100% / 100% / 97% Overall: 89% / 94% / 92% / 89% There was a statistically significant difference in the estimate of 5-year biochemical negative survival between the risk factor groups ($p < 0.0001$), although there was no difference based on cases receiving hormone treatment or not. Disease recurrence in 15% (32/214) to last follow-up. 2% (5/214) of cases died from prostate cancer.	**Complications** Early complications Complication / Rate Postoperative fever: 1% (3/214) Transient haematuria: 17% (36/214) Perineal paraesthesia (resolved spontaneously): 1% (3/214) Late complications These were rated severe where hospitalisation or surgery required or total impotence, moderate if medical therapy required, and mild if no treatment required Actuarial 5-year complication Complication / Rate Severe Urological: 10% Gastrointestinal: 0% Sexual dysfunction: 14% Moderate Urological: 26% Gastrointestinal: 17% Sexual dysfunction: 41% Mild Urological: 45% Gastrointestinal: 24% Sexual dysfunction: 55% Erectile dysfunction was statistically higher in case treated with endocrine therapy, compared to those who were not ($p = 0.02$)	Prospective follow-up for PSA outcomes, but retrospective evaluation of medical records for complications. Midway through the series the EBRT clinical target was restricted to the prostate only rather than the pelvic lymph nodes too.

Abbreviations used: RP, radical prostatectomy; EBRT/XRT, external beam radiation; CRT, conformal radiotherapy; bRFS, biochemical relapse free survival; bDFS, biochemical disease free survival; QOL, quality of life; LDR, low dose rate brachytherapy; BED, biologically effective dose.

Study details	Key efficacy findings	Key safety findings	Comments
Deger S (2002)[4] Case series Germany December 1992 – December 1997 n = 230 patients with T1–T3 localised prostate cancer. Mean age was 67.3 years (range 49–83 years) Initial median PSA value was 12.8 ng/ml Follow-up = 40 months (median) Disclosure of interest: not stated	**Progression-free survival** PSA decreased from a median value of 12.8 ng/ml at baseline to 0.18 ng/ml at 60 months Five-year overall survival was 93% and disease-specific survival was 98% At 1 year no residual tumours were seen in 50% of the biopsy specimens (n = 128). At 2 years no tumours were seen in 68% of the biopsy specimens (n = 77).	**Complications** No grade 4 Radiation Therapy Oncology Group (RTOG) complications occurred. 3 patients experienced haematuria. 28 patients (12.2%) had late grade 3 and 4 complications. 17 patients (7.4%) developed urethral strictures. 7 patients (3%) suffered from grade 2–3 incontinence. 4 patients (1.7%) developed a recto-urethral fistula.	Primary cancer (localised) Previous therapy not stated. Combination therapy. High dose brachytherapy as a boost – combination with EBRT. Progression was defined as three consecutive PSA rises. Interstitial dose/EBRT dose varied depending on timing of treatment and stage of prostate cancer. Authors note that initial PSA value < 10 ng/ml, low stage and low grade were significantly related to 5-year progression-free survival. Authors note that the complication rate decreased after modifying the treatment technique; also those that had received TURP had a greater complication rate.

Abbreviations used: RP, radical prostatectomy; EBRT/XRT, external beam radiation; CRT, conformal radiotherapy; bRFS, biochemical relapse free survival; bDFS, biochemical disease free survival; QOL, quality of life; LDR, low dose rate brachytherapy; BED, biologically effective dose.

Study details	Key efficacy findings	Key safety findings	Comments
Syed AMN (2001)[8] Case series USA n = 200 June 1996 to July 1999 Patients with biopsy-proven, clinically localised carcinoma of the prostate Age = 64 years, PSA = 10 ng/ml, Stage T1c = 28, T2a = 65, T2b = 64,T3a-b = 43. 22 to 26 Gy of HDR brachytherapy in 4 fractions, and 39.6 to 45 Gy EBR (depending on stage of tumour). 70% of patients had HDR brachytherapy before and 30% after EBRT. 3D CT scanning for planning. 72 high-risk cases had concomitant hormone therapy. Follow-up = 30 months. Disclosure of interest: no significant relationship exists between authors and companies whose products are referenced in the study.	**Survival** Clinical control was achieved in 97% (194/200) of patients. One patient died of locally persistent tumour, and one from pulmonary metastasis. Overall disease-specific survival (clinical and PSA relapse free) was 97% (194/200) to 25 months follow-up. **Biochemical survival** Average PSA fell from 10 to 1.1 ng/ml. 85% (170/200) achieved PSA nadir < 1 ng/ml.	**Complications** Acute grade 4 toxicity occurred in 10%. Acute grade 3 toxicity occurred in 20% of patients. Complication — Rate Blood in ejaculation (up to 3 months) — 10% (20/200) Urethral strictures — 1.5% (3/200) Incontinence — < 1% (1/200) In patients who were potent at baseline, impotency occurred in 30% who did not receive androgen blockade	A diverse study sample in terms of tumour stage. Survival outcomes were not reported separately for subgroups with or without hormone treatment. It was not stated how many investigators undertook the procedures. The radiation delivered varied across stage of cancer. No loss to follow-up reported.

Abbreviations used: RP, radical prostatectomy; EBRT/XRT, external beam radiation; CRT, conformal radiotherapy; bRFS, biochemical relapse free survival; bDFS, biochemical disease free survival; QOL, quality of life; LDR, low dose rate brachytherapy; BED, biologically effective dose.

Study details	Key efficacy findings	Key safety findings	Comments
Pellizzon et al. (2003)[7] (2004)[9] Brazil Case series March 1997 – March 2000 108 patients with biopsy-proven prostate cancer (11 patients were excluded or lost to follow-up). EBRT of 45 Gy in 1.8 Gy fractions over 5 weeks, followed by HDR brachytherapy in 4 or 5 Gy fractions of 16 Gy for low risk and 20 Gy for high-risk patients. Median age: 68 years (range 56–83 years), PSA = 15.3 ng/ml. Median follow-up:44 months (range 36–72 months) (in 2004 report). Disclosure of interest: not stated.	**Outcomes reported:** biochemical control PSA failure occurred in 33 (30.5%) patients in a median interval of 18.3 (range 8–28 months). Crude biochemical control for all patients over 48 months was 69.5%. Actuarial 4-year biochemical control was 75.3%.	**Complications**: Acute gastrointestinal toxicity (RTOG) and urinary 11 patients (10.2%) had a grade 1–2 toxicity Acute gastrourinary toxicity 20 patients (18.5%) had grade 1–2 toxicity Late gastrointestinal toxicity (RTOG) and urinary 13 patients (12%) had a grade 1–2 toxicity Late gastrourinary toxicity 5 patients (4.6%) had grade 1–2 toxicity 5-year actuarial urinary retention free survival was 86.2% (from 2004 paper)	Primary cancer not stated All patients had previous androgen deprivation, and all treatment in combination with EBRT High dose brachytherapy as a boost – combination with EBRT. Patients were divided between low-risk group and high-risk group. Some patients also had a course of hormonal therapy. The treatment consisted of a total dose of 45 Gy in 1.8 Gy per fraction for 5 weeks.

Abbreviations used: RP, radical prostatectomy; EBRT/XRT, external beam radiation; CRT, conformal radiotherapy; bRFS, biochemical relapse free survival; bDFS, biochemical disease free survival; QOL, quality of life; LDR, low dose rate brachytherapy; BED, biologically effective dose.

Study details	Key efficacy findings	Key safety findings	Comments
Lennernas B (2002) Case series Sweden n = 50 1988 to 1995 Patients with confirmed or assumed localised disease and prostate< 60 cm^2 EBRT in 2 Gy fractions with total 50 Gy. HDR brachytherapy with US guidance in two 10 Gy fractions (between EBRT periods) Age = 64 years, Stage T1 = 6, T2 = 33, T3 = 11, hormone therapy = 8%, PSA = 12.6 ng/ml Follow-up = 7.2 years Disclosure of interest: supported by charity grant.	**Survival** 16% (8/50) of patients died, 8% (4/50) due to prostate cancer at 7.2 years follow-up. **Biochemical outcome** 5% (2/42) of survivors had PSA > 1 ng/ml **Biopsy findings** There was no evidence of viable cancer in 86% (36/42) of cases on prostate biopsy.	**Complications** Grade 3 or 4 toxicity Urinary incontinence and outflow obstruction refractory to conservative treatments was reported in 5% (2/41) Prostate sclerosis 2% (1/41) Faecal incontinence 2% (1/41) Other toxicity 25% of cases suffered from mild faecal symptoms (mostly diarrhoea). (absolute figures not presented) **Potency** 24% (10/41) of cases were potent at follow-up	Patients likely to be included in Astrom (2005). In two patients only one HDR brachytherapy treatment was delivered due to technical difficulties and these cases received extra EBRT. Patients who were lost to follow-up or moved outside the country were not included in analysis. One investigator contacted all cases to evaluate clinical outcomes. PSA outcome only analysed in survivors. Selected cohort of patients treated at the only centre in Sweden offering HDR brachytherapy at the time. Authors note HDR brachytherapy has a marked learning curve, and the study reports on the first 50 cases treated.

Validity and generalisability of the studies

- One of the controlled trials included in Table 2 includes cases in the active arm that are included in case series elsewhere.
- Most studies use HDR brachytherapy in combination with EBRT. The order in which each is given also varies between studies.
- Some studies also use hormone therapy in combination with HDR.
- The HDR brachytherapy dose delivered to the rectum varies between studies depending on treatment planning.
- There is some variation in the definitions used for staging, and for complications.

Specialist advisors' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College.

Mr A Flynn, Dr D Ash, Mr M Emberton, Dr P Hoskin

- All specialist advisors considered the procedure to be established and no longer new, when used in combination with external beam radiation therapy. However, as a monotherapy it is still investigational.
- The benefits of the procedure may include improved biochemical and overall survival, and reduced side effects compared to other treatments.
- Theoretical adverse events may include urethritis, urethral stricture, proctosis causing constipation, incontinence, acute retention, impotence, haematuria, haematospermia, and bladder, rectal and sphincter injuries including possible recto-urethral fistula.
- Additional reported events include bleeding and infection.
- There is some controversy regarding patient selection criteria, but while the procedure is reserved for high-risk patients the impact on the NHS is likely to be small. It is likely to be used in fewer than 10 specialist centres.
- There are few safety concerns, but potential movement of needles between treatment fractions may require re-imaging and repositioning.
- Undertaking the procedure requires brachytherapy experience and mentoring in this technique, with ultrasound guidance and an understanding of the physics of dose planning.
- The procedure should be offered as part of a multidisciplinary group, involving a clinical oncologist, urologist, radiologist, medical physicist/dosimetrist, and therapeutic radiographer.
- There are no randomised controlled trials to date demonstrating efficacy outcomes, but a UK study should report in 2 to 3 years on PSA relapse-free survival.

Issues for consideration by IPAC

- The Lennernas paper was included despite reporting on the same patients as the Alstrom (2005) paper as it provided long-term clinical follow-up.
- The Pellizzon papers are combined in one table as they represent the same cohort.
- A inclusion threshold for case series in Table 2 was used with n < 100, and/or follow-up < 50 months. Many additional studies that fitted the clinical inclusion criteria are included in appendix A

References

1 Kestin LL, Martinez AA, Stromberg JS et al. (2000) Matched-pair analysis of conformal high-dose-rate brachytherapy boost versus external-beam radiation therapy alone for locally advanced prostate cancer. *Journal of Clinical Oncology* 18(15):2869–80.

2 Galalae RM, Martinez A, Mate T et al. (2004) Long-term outcome by risk factors using conformal high-dose-rate brachytherapy (HDR-BT) boost with or without neoadjuvant androgen suppression for localized prostate cancer. *International Journal of Radiation Oncology, Biology, Physics.* 58(4)*:*1048–55.

3 Strom L, Pedersen D, Mercke C et al. (2005) Long-term outcome of high dose rate brachytherapy in radiotherapy of localised prostate cancer. *Radiotherapy & Oncology* 74(2):157–61.

4 Deger S, Boehmer D, Turk I et al. (2002) High dose rate brachytherapy of localized prostate cancer. *European Urology* 41(4):420–6.

5 Lennernas B, Holmang S, Hedelin H (2002) High-dose rate brachytherapy of prostatic adenocarcinoma in combination with external beam radiotherapy: a long-term follow-up of the first 50 patients at one center. *Strahlentherapie und Onkologie* 178(10):537–41.

6 Grills IS, Martinez AA, Hollander M et al. (2004) High dose rate brachytherapy as prostate cancer monotherapy reduces toxicity compared to low dose rate palladium seeds. *Journal of Urology* 171(3):1098–1104.

7 Pellizzon ACA, Nadalin W, Salvajoli JV et al. (2003) Results of high dose rate afterloading brachytherapy boost to conventional external beam radiation therapy for initial and locally advanced prostate cancer. *Radiotherapy & Oncology* 66(2):167–72.

8 Nisar Syed AM, Puthawala A, Sharma A et al. (2001) High-dose-rate brachytherapy in the treatment of carcinoma of the prostate. *Cancer Control* 8(6):511–21.

9 Pellizzon ACA, Salvajoli JV, Maia MAC et al. (2004) Late urinary morbidity with high dose prostate brachytherapy as a boost to conventional external beam radiation therapy for local and locally advanced prostate cancer. *Journal of Urology* 171(3):1105–08.

Appendix A: Additional papers on high dose rate brachytherapy for prostate cancer not included in summary table 2

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (Table 2). It is by no means an exhaustive list of potentially relevant studies.

Article title	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in Table 2
Bezou AR, Monsour P, Buhler C, Sloan C. High dose rate afterloading 192 iridium prostate brachytherapy. *Journal of the Louisiana State Medical Society* 154(1):37	n=60 FU=14 months	2/60 PSA failures at 14months. No significant operative or postoperative complications occurred	Have larger series and longer follow up in table 2
Borghede G, Hedelin H, Holmang S, Johansson KA, Aldenborg F, Pettersson S et al. Combined treatment with temporary short-term high dose rate iridium-192 brachytherapy and external beam radiotherapy for irradiation of localized prostatic carcinoma. Radiotherapy & Oncology Vol 44(3)()(pp 237-244), 1997 1997;(3):237-244.	n=50 FU=45 months	Clinical and biopsy confirmed local control in 96% (48/50) casesPSA level <1 ng/ml seen in 84% of patients	Have larger series in table 2
Chiang PH, Fang FM, Jong WC, Yu TJ, Chuang YC, Wang HJ. High-dose rate iridium-192 brachytherapy and external beam radiation therapy for prostate cancer with or without androgen ablation. International Journal of Urology Vol 11(3)()(pp 152-158), 2004 2004;(3):152-158	n=42 FU=17 months	No PSA failure noted during follow up	Have larger series and longer follow up in table 2
Curran MJ, Healey GA, Bihrle IW, Goodman N, Roth RA. Treatment of high-grade low-stage prostate cancer by high-dose-rate brachytherapy. Journal of Endourology Vol 14(4)()(pp 351-356), 2000 2000;(4):351-356	n=61 FU=12 months	One case died from prostate cancer during follow up, and 3 confirmed treatment failures	Have larger series and longer follow up in table 2
Dinges S, Deger S, Koswig S, Boehmer D, Schnorr D, Wiegel T et al. High-dose rate interstitial with external beam irradiation for localized prostate cancer - Results of a prospective trial. Radiotherapy & Oncology Vol 48(2)()(pp 197-202), 1998 1998;(2):197-202	n=82 FU=24 months	PSA <1 ng/ml in 53% of cases at 2 years	Have larger series and longer follow up in table 2
Egawa S, Shimura S, Irie A, Kitano M, Nishiguchi I, Kuwao S et al. Toxicity and health-related quality of life during and after high dose rate brachytherapy followed by external beam radiotherapy for prostate cancer. Japanese Journal of Clinical Oncology Vol 31(11)()(pp 541-547), 2001 2001;(11):541-547.	n=58 FU=10 months	Rectal bleeding (of various degrees) due to rectal proctosis was seen in 22% of patient sat a median time of 11 months	Have larger series and longer follow up in table 2

Fujioka H, Ishimura T, Sakai Y et al. Erectile function after brachytherapy with external beam radiation for prostate cancer. *Archives of Andrology* 50(4):295	n=42 FU=12 months	Erectile score fell from 15.8 to 9.6 points at 3 months (p=0.054) and 11.3 at 12 months (p=0.06)	Have larger series and longer follow up in table 2
Galalae RM, Loch T, Riemer B, Rzehak P, Kuchler T, Kimmig B et al. Health-related quality of life measurement in long-term survivors and outcome following radical radiotherapy for localized prostate cancer. Strahlentherapie und Onkologie Vol 180(9)()(pp 582-589), 2004 2004;(9):582-589	n=145 FU=78 months	86% of patients disease free, and 78% biochemically controlled at 6.5 years follow up	Same cases as Galalae (2004)
Galalae RM, Martinez A, Mate T, Mitchell C, Edmundson G, Nuernberg N et al. Long-term outcome by risk factors using conformal high-dose-rate brachytherapy (HDR-BT) boost with or without neoadjuvant androgen suppression for localized prostate cancer. International Journal of Radiation Oncology, Biology, Physics Vol 58(4)()(pp 1048-1055), 2004 Date of Publication: 15 MAR 2004 2004;(4):1048-1055	n=144 FU=96 months	Overall survival 72%, disease free survival was 83% to 8 years	Same cases as Galalae (2004)
Harada T, Kigure T, Yuri Y et al. Local control of prostate cancer with transurethral intracavitary radiation therapy. *Radiation Medicine* 11(4):139	n=13 FU=35 months	Serious complications were not evident during follow up	Have larger series in table 2
Hiratsuka J, Jo Y, Yoshida K, Nagase N, Fujisawa M, Imajo Y. Clinical results of combined treatment conformal high-dose-rate iridium-192 brachytherapy and external beam radiotherapy using staging lymphadenectomy for localized prostate cancer. International Journal of Radiation Oncology, Biology, Physics Vol 59(3)()(pp 684-690), 2004 Date of Publication: 01 JUL 2004 2004;(3):684-690.	n=71 FU=44 months	69/71 cases still alive at final follow up. 85% of cases achieved PSA nadir <1 ng/ml	Have larger series in table 2
Jo Y, Hiratsuka J, Fujii T, Takenaka A, Fujisawa M. High-dose-rate iridium-192 afterloading therapy combined with external beam radiotherapy for T1c-T3bN0M0 prostate cancer. Urology Vol 64(3)()(pp 556-560), 2004 2004;(3):556-560	n=98 FU=43 months	Overall biochemical disease free survival was 96% at 2 years and 93% at 5 years	Have larger series in table 2
Lev EL, Eller LS, Gejerman G et al. (2004) Quality of life of men treated with brachytherapies for prostate cancer. *Health and Quality of Life Outcomes* 2(1):28.	n=67 (HDR) FU=? Non randomised controlled study	Treatment effect size predicted quality of life scores on SF-36 scale	Intervention and comparator not well defined
Martin T, Baltas D, Kurek R et al. 3-D Conformal HDR brachytherapy as monotherapy for localized prostate cancer: a pilot study. *Strahlentherapie*	n=52 FU=8 months	Grade 3 genitourinary toxicity in 4% (2/52) of cases	Same cases as Martin (2004)

und Onkologie 180(4):225–232.			
Martin T, Roddiger S, Kurek R et al. 3D conformal HDR brachytherapy and external beam irradiation combined with temporary androgen deprivation in the treatment of localized prostate cancer. *Radiotherapy and Oncology* 71(1):35–41.	n=102 FU=30 months	Actuarial biochemical control rate was 87% at 2 years and 82% at 3 years. Overall survival was 90% at 3 years.	Have larger series in table 2
Mate TP. High dose rate prostate brachytherapy with ^{192}iridium: the Seattle experience. *Nowotwory* 53(1):34.	n=104 FU=76 months	77% of cases biochemically no evidence of disease up to 10 years of follow up	Little information on study design and therefore possibly of low quality
Paul R, Hofmann R, Schwarzer JU, Stepan R, Feldmann HJ, Kneschaurek P et al. Iridium 192 high-dose-rate brachytherapy--a useful alternative therapy for localized prostate cancer? World Journal of Urology 15(4):252-6, 1997.	n=40 FU=130	80% of cases show no evidence of disease or stable disease	Have larger studies, and cases were selected as those not suitable for radical prostatectomy
Serin M, Erkal HS, Sak SD et al. High dose rate transurethral brachytherapy as a boost dose for localized adenocarcinoma of the prostate. *Urologia Internationalis* 58(1):30	n=11 FU=30 months	Local control was achieved in all patients. PSA levels were normalised in all cases by 6 months	Have larger series and longer follow up in table 2
Stevens MJ, Stricker PD, Saalfeld J et al. (2003) Treatment of localized prostate cancer using a combination of high dose rate iridium-192 brachytherapy and external beam irradiation: initial Australian experience. *Australasian Radiology* 47(2):152–160.	n=82 FU=36 months	PSA progression free survival was 91%, and complications were low	Have larger series and longer follow up in table 2
Stromberg J, Martinez A, Gonzalez J et al. (1995) Ultrasound-guided high dose rate conformal brachytherapy boost in prostate cancer: treatment description and preliminary results of a phase I/II clinical trial. *International Journal of Radiation Oncology Biology Physics* 33(1):161–171.	n=58 (HDR) FU=26 months Non randomised controlled trial	The biochemical control rate was significantly higher in the group with HDR compared to EBRT alone	Same cases as Kestin (2000)
Stromberg JS, Martinez AA, Horwitz EM et al. (1997) Conformal high dose rate iridium-192 boost brachytherapy in locally advanced prostate cancer: superior prostate-specific antigen response compared with external beam treatment. *Cancer Journal From Scientific American* 3(6):346–352.	n=33 FU=13 months	No significant intraoperative or peri operative complications occurred. 9% of cases suffered grade 3 toxicity, two dysuria and one case of diarrhoea)	Have larger series and longer follow up
Syed AMN, Puthawala AA, Barth N et al. (1997) High dose rate brachytherapy in the treatment of carcinoma of the prostate: preliminary results. *Journal of Brachytherapy International* 13(4):315–331.	n=40 FU=?	All patients tolerated treatment without significant morbidity or early complications	Have larger series in table 2
Wahlgren T, Brandberg Y, Haggarth L	n=93	Health related	Have larger series

et al. (2004) Health-related quality of life in men after treatment of localized prostate cancer with external beam radiotherapy combined with ^{192}Ir brachytherapy: a prospective study of 93 cases using the EORTC questionnaires QLQ-C30 and QLQ-PR25. *International Journal of Radiation Oncology Biology Physics* 60(1):51–9.	FU=18 months	quality of life were generally high and did not change over time	and longer follow up in table 2
Yoshioka Y, Nose T, Yoshida K et al. (2000) High-dose-rate interstitial brachytherapy as a monotherapy for localized prostate cancer: treatment description and preliminary results of a phase I/II clinical trial. *International Journal of Radiation Oncology Biology Physics* 48(3):675–81.	n=22 FU=31 months	No significant peri- or post operative events occurred. No grade 3 toxicity. Four year biochemical relapse free survival was 55%	Same cases as Yoshioka (2003)
Yoshioka Y, Nose T, Yoshida K et al. (2003) High-dose-rate brachytherapy as monotherapy for localized prostate cancer: a retrospective analysis with special focus on tolerance and chronic toxicity. *International Journal of Radiation Oncology Biology Physics* 56(1):213–20.	n = 43 FU = 24 months	3-year actuarial overall survival, local control and biochemical no evidence of disease rates were 94%, 100% and 55% respectively	Have larger series and longer follow-up

Appendix B: Related published NICE guidance for high dose rate brachytherapy for prostate cancer

Guidance	Recommendation
Interventional procedure	1.1 Current evidence on the safety and short- to medium-term efficacy of low dose rate brachytherapy 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. 1.2 Most of the evidence on the efficacy of low dose rate brachytherapy for localised prostate cancer relates to the reduction of prostate-specific antigen (PSA) levels and to biopsy findings. The effects on quality of life and long-term survival remain uncertain. Clinicians should ensure that patients understand these uncertainties and the alternative treatment options. Use of the Institute's *Information for the public* is recommended. 1.3 A multidisciplinary team should be involved in the planning and use of this procedure. The Institute has issued a cancer service guideline on *Improving Outcomes in Urological Cancers* (www.nice.org.uk/csguc). 1.4 Further research and audit should address quality of life, clinical outcomes and long-term survival.
Technology appraisals	N/A
Clinical guidelines	N/A
Public health	N/A

Appendix C: Literature search for high dose rate brachytherapy for prostate cancer

Procedure Number: 309 Date Completed: 21/03/2005	Procedure Name: High dose rate brachytherapy for prostate cancer

Action	Comments	Version searched (if applicable)	Date searched
Search for similar NICE topics	251 was originally looking at both low and high dose rate but was split		18/03/2005
Consult notification and specialist advisors questionnaires for additional papers	None found		18/03/2005
Conduct general internet search for background	A good overview of high dose rate brachytherapy		18/03/2005
Search for Cochrane systematic review	No systematic review found	2005 Issue 1	18/03/2005
ASERNIP website	Nothing relevant found		18/03/2005
FDA website	Nothing relevant found		18/03/2005
Search conferences websites	News item found with research poster another poster		
Search Databases:			
The Cochrane Library	5 records found	2005 Issue 1	21/03/2005
CRD Databases	28 records found		21/03/2005
Embase	132 records found	1980 – 2005 Week 11	18/03/2005
Medline	167 records found	1966 - March Week 2 2005	18/03/2005
Premedline	6 records found	March 17 2005	18/03/2005
CINAHL	12 records found	1982 - date	21/03/2005
BLIC (limit to current year only)	8 records found	Limited from 2004	21/03/2005
National Research Register	2 records found	2005 Issue 1	21/03/2005
Controlled Trials Registry	11 records found		21/03/05

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in other databases.

Procedure Number: 309	**Procedure Name: High Dose rate brachytherapy for prostate cancer**
Database: Medline 1966 - March Week 2 2005	**Date searched: 18/03/2005**

1. brachytherapy/
2. brachytherap$.tw.
3. 1 or 2
4. (high adj2 dose adj2 rate).tw.
5. hdr.tw.
6. (iridium adj2 "192").tw.
7. ir-192.tw.
8. or/4-7
9. 3 and 8
10. Prostatic Neoplasms/
11. (prostat$ adj3 neoplasm$).tw.
12. (prostat$ adj3 cancer$).tw.
13. (prostat$ adj3 carcinoma$).tw.
14. (prostat$ adj3 tumo?r$).tw.
15. (prostat$ adj3 adenocarcinoma$).tw.
16. or/10-15
17. 9 and 16