Review of Interim Funded Service: *Brachytherapy for the treatment of prostate cancer*

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MSAC application 1089.1

Assessment report

Review of Interim Funded Service: Brachytherapy for the Treatment of Prostate Cancer

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

The MSAC's recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared by Mr David Tamblyn, Mr Ben Ellery and Ms Tracy Merlin from Adelaide Health Technology Assessment (AHTA), Discipline of Public Health, the University of Adelaide, with the assistance of an Advisory Panel of experts. The report was commissioned by the Department of Health and Ageing on behalf of the Medical Services Advisory Committee (MSAC). It was edited by Ms Jo Mason, Mason Edit, South Australia.

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Medical Services Advisory Committee—role and approach

The Medical Services Advisory Committee (MSAC) was established by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. The MSAC advises the Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

Assessment of low-dose-rate brachytherapy

Purpose of application

The review of the interim Medicare Benefits Schedule (MBS) listing of low-dose-rate (LDR) brachytherapy (BT) for men with localised prostate cancer was requested by the Australian Department of Health and Ageing. This assessment of the safety, effectiveness and cost-effectiveness of LDRBT follows Application 1029 (Medical Services Advisory Committee 2000), which resulted in the interim listing of LDRBT on the MBS, and Application 1089 (Medical Services Advisory Committee 2005), which resulted in the continued interim listing on the MBS.

LDRBT, or permanent seed BT, is the implantation of radioisotopes (iodine-125 or palladium-103) directly into the prostate gland for the treatment of localised prostate cancer. The procedure is performed under transrectal ultrasound guidance and may require an overnight stay in hospital. Before implantation—either 1 week or so before, or sometimes during, the procedure—the distribution of radioactive seeds is planned to ensure adequate distribution of radiation throughout the prostate. The distribution of the seeds is then verified at another visit (often 1 month later) using computerised tomography to identify any seed migration. The procedure requires the expertise of a radiation oncologist, urologist, radiation therapist and radiation physicist.

While LDRBT may be delivered in combination with external beam radiotherapy (EBRT), this report analysed only LDRBT used alone. In addition, the review has only considered evidence regarding LDRBT delivered using iodine-125 radioactive seeds, as other radioisotopes used in the procedure are not available in Australia.

LDRBT is currently listed on the MBS for men with localised, low- to intermediate-risk prostate cancer. Specifically, to qualify for reimbursement, men must have a prostate specific antigen (PSA) level of ≤ 10 ng/mL, a tumour with a clinical stage of T1 or T2 (confined to the prostate) and a Gleason score of ≤ 7.

A rigorous assessment of evidence is the basis of decision making when public funding is sought. A team from Adelaide Health Technology Assessment in the Discipline of Public Health, School of Population Health and Clinical Practice within the University of Adelaide, was commissioned by the Department of Health and Ageing to conduct a systematic review of the literature on the use of LDR ^{125}I BT for the treatment of localised prostate cancer. An advisory panel with expertise in this area provided advice to

the MSAC to assist with this evaluation of the safety, effectiveness and cost-effectiveness of LDRBT for the treatment of localised prostate cancer.

Current arrangements for public reimbursement

LDRBT currently receives interim funding through the MBS, which provides reimbursement for professional fees and services associated with the procedure. The substantial cost of the BT seeds is covered by private health insurance but is not universally funded by state/territory governments for patients accessing the technology through the public healthcare system.

Item 15338
PROSTATE, radioactive seed implantation of, radiation oncology component, using transrectal ultrasound guidance, for localised prostatic malignancy at clinical stages T1 (clinically inapparent tumour not palpable or visible by imaging) or T2 (tumour confined within prostate), with a Gleason score of less than or equal to 7 and a prostate specific antigen (PSA) of less than or equal to 10ng/ml at the time of diagnosis. The procedure must be performed at an approved site in association with a urologist.
Fee: $884.25 **Benefit:** 75% = $663.20 85% = $815.15
Item 37220
PROSTATE, radioactive seed implantation of, urological component, using transrectal ultrasound guidance, for localised prostatic malignancy at clinical stages T1 (clinically inapparent tumour not palpable or visible by imaging) or T2 (tumour confined within prostate), with a Gleason score of less than or equal to 7 and a prostate specific antigen (PSA) of less than or equal to 10ng/ml at the time of diagnosis. The procedure must be performed by a urologist at an approved site in association with a radiation oncologist, and be associated with a service to which item 55603 applies.
Fee: $986.90 **Benefit**: 75% = $740.20
Item 15539
BRACHYTHERAPY PLANNING, computerised radiation dosimetry for ^{125}I seed implantation of localised prostate cancer, in association with item 15338
Fee: $592.90 **Benefit**: 75% = $444.70 85% = $523.80

Source: http://www9.health.gov.au/mbs/search.cfm (MBS Online - accessed 29 October 2010)

Background

LDRBT has been considered by the MSAC on two previous occasions. In 2000 the MSAC recommended the interim funding of LDRBT for the treatment of men with localised prostate cancer with a Gleason score ≤ 6 and a PSA ≤ 10 ng/mL. This recommendation was accepted by the Minister for Health and Aged Care on 9 February 2001. In 2005 the MSAC recommended the continuation of interim funding of LDRBT for the treatment of localised prostate cancer within the same population. This recommendation was accepted by the Minister for Health and Ageing on 28 November 2005.

In 2006 an application was made by the Australian and New Zealand Association of Urological Surgeons (ANZAUS) to have the eligibility criteria for MBS reimbursement expanded to include men with Gleason scores of 7. A critique of the studies submitted by ANZAUS to support this revision was undertaken by the National Health and Medical Research Council (NHMRC) Clinical Trials Centre. The studies were assessed as being supportive of extending the Gleason score cut-off for MBS reimbursement from 6 to 7; however, evidence was not sought or appraised systematically. This recommendation was accepted by the Minister for Health and Ageing, and the MBS reimbursement criteria was altered in the July 2007 supplement (Medicare Australia 2007).

Clinical need

Prostate cancer is the most commonly diagnosed cancer in Australian men (excluding non-melanocytic skin cancer). In 2006, 17,444 new cases of prostate cancer were diagnosed in Australia and 2,952 deaths were attributed to the disease. Age-standardised incidence rates have been increasing since 2000 following a peak of 184.3 per 100,000 men (age standardised to the 2001 Standard Australian Population) in 1994, which was largely attributed to the introduction of PSA testing.

Currently, almost one in seven men will be diagnosed with prostate cancer before the age of 75 years and more than one in five men before the age of 85 years. Due to greater awareness of the disease and the introduction of PSA testing, many men will be identified with localised prostate cancer, and will potentially be amenable to curative treatments.

Prostate cancer is a heterogeneous disease ranging from indolent and unlikely to pose a threat to a man in his lifetime, to aggressive and life threatening. There are several known prognostic markers—such as PSA level (or rate of change), clinical stage and Gleason score—which may help identify more aggressive cancers. However, despite considerable effort in the area of risk assessment, substantial uncertainty still remains regarding the determination of which cancers require intervention and the most appropriate timing of the intervention.

Perhaps as a result of earlier detection of, or innovations in treatment for, prostate cancer, the age standardised mortality rate is steadily falling, from 43.7 per 100,000 in 1993 to 31.0 per 100,000 in 2007. Despite a decline in mortality rates, prostate cancer remains an important disease, responsible for more deaths than any other cancer in men with the exception of lung cancer.

It is estimated that 5,000 men will be eligible for LDRBT in 2010 and 1,400 procedures will be performed. This represents an increase of about 400 procedures from the most recent data available in the 2007–08 financial year. The number of LDRBT procedures will be contingent upon access to a radiotherapy centre offering the procedure, as well as the community preference for LDRBT in comparison to competing procedures such as external beam radiotherapy, radical prostatectomy and active surveillance.

Comparators

Three comparators were identified for this review with respect to treatment for localised prostate cancer—external beam radiotherapy (EBRT), radical prostatectomy (RP) and active surveillance (AS).

Radical prostatectomy

RP is the surgical removal of the entire prostate gland, which can be performed either as an open procedure or laparoscopically. More recently, robot-assisted laparoscopic techniques have been developed and are available in certain centres around Australia.

RP is an invasive procedure requiring anaesthetic and is not offered to men with significant comorbidities due to the risk imposed by the surgery. It is not often offered to men over the age of 75 years.

External beam radiotherapy

EBRT is the irradiation of the prostate gland, typically with high-energy photons from a linear accelerator. EBRT is delivered as an outpatient procedure over a period of 6–8 weeks. The duration of each treatment session is about 10 minutes, and most of the time is required for preparation.

EBRT is a relatively non-invasive procedure, although modern techniques may require the implantation of tiny markers (usually three) in the prostate to enable accurate targeting of the radiotherapy.

Active surveillance

AS is the close monitoring of men with prostate cancer, who would otherwise be eligible for curative treatment, for signs of progression or advancing disease. The aim of AS is to delay treatment, perhaps indefinitely, or until it is clear that the patient has a type of prostate cancer that is not indolent or insignificant.

It is not clear how commonly AS is practised in Australia; however, its use is growing overseas.

Safety

A total of 14, 16, 11 and 11 comparative studies (level II to III-3 evidence) reported on the urinary side effects, bowel side effects, sexual dysfunction and health-related quality of life of patients receiving low-dose-rate brachytherapy (LDRBT) compared with external beam radiotherapy (EBRT), radical prostatectomy (RP) or active surveillance (AS).

Key results

Irritative or obstructive urinary symptoms

The most common side effect associated with the treatment of prostate cancer with LDRBT is a transient increase in irritative (painful urination, urinary frequency, urgency) and obstructive (difficulty passing urine, dribbling and urinary retention) symptoms. In all included studies comparing LDRBT and RP, urinary irritation was greater following LDRBT than RP, with four studies showing an enduring difference between the treatments beyond 1 year. As reported by the only randomised controlled trial, there was no difference in irritative or obstructive symptoms at 5 years compared with baseline symptoms in men receiving either LDRBT or RP.

Compared with EBRT, two studies reported worse urinary irritation following LDRBT and two reported no difference. Only one study comparing EBRT with LDRBT controlled for baseline urinary function and this found no difference in irritative or obstructive symptoms between the groups.

No study compared irritative or obstructive symptoms following LDRBT with AS.

Urinary incontinence

Urinary incontinence was less common following LDRBT than following RP. Incontinence (or the need to wear incontinence pads) was consistently higher in the RP group beyond 3 years following treatment. Incontinence was worse immediately

following treatment, and was reported by 68% of men receiving RP and 17% of men receiving LDRBT. By 3 years following treatment, reported differences between the treatment groups were modest, with 12% of men treated with RP and 7% treated with LDRBT continuing to experience incontinence.

Four studies comparing urinary incontinence following LDRBT and EBRT reported no difference; however, one study reported an increase in usage of pads among men treated with LDRBT at 1 month. By 3 years, incontinence was reported by 2.7% of men treated with EBRT.

Only one study reported on incontinence rates among men managed with AS, with 3.4% of men requiring pads at 3 years. However, a proportion of men recorded as receiving AS at baseline had opted for active treatment, and the rate of incontinence is likely to be contingent upon the effect of the chosen treatment.

Urethral stricture

There was substantial heterogeneity of urethral stricture rates among studies involving LDRBT. Urethral stricture was reported in 0.15–14% of men receiving LDRBT, 6.5% receiving RP and 2% receiving EBRT. No study reported on the rates of urethral stricture in men managed with AS. Due to the variability of urethral stricture rates reported in the evidence, it is difficult to draw conclusions regarding the comparative safety of treatments for this outcome.

Urinary retention

One randomised controlled trial reported urinary retention in 10% of men following treatment with LDRBT, compared with none following RP. One study comparing LDRBT and EBRT reported that 15% of LDRBT patients required catheterisation following treatment, compared with none among the EBRT arm. No study reported on the rates of urinary retention among men managed with AS.

Bowel motion frequency

One study reported an increase in men with a 'moderate or big problem' due to increased frequency of bowel movements following both LDRBT and EBRT. However, at 16 months following treatment, only 2% of men treated with LDRBT continued to report a 'moderate or big problem', compared with 12% of men treated with EBRT. No study involving either RP or AS reported on frequency of bowel motions.

Faecal incontinence

One study reported an increase in faecal incontinence from baseline in 9% of men following LDRBT and 2% following RP. However, the definition of faecal incontinence was not reported and it is unclear whether very minor incidents were included. This is important because infrequent and minor uncontrolled passage of faeces has little effect on quality of life, whereas frequent or complete faecal incontinence is a major detriment to quality of life. It is therefore difficult to draw conclusions regarding this outcome. No study reported on faecal incontinence following EBRT or AS.

Rectal bleeding

One study reported an increase in rectal bleeding following EBRT from 8% of men at baseline to 17% at 16 months, compared with no increase among men who received LDRBT (remaining at 12% as per baseline). In another study a potentially contrasting result was reported, with 15% of men who received LDRBT reporting an increase in

rectal bleeding at 2 years. These results are difficult to reconcile. No increase in rectal bleeding was reported among men treated with RP, and no study reported on rectal bleeding in men managed with AS.

Erectile dysfunction

Erectile dysfunction is far more common following RP than LDRBT. Despite higher rates of potency at baseline in men selecting nerve-sparing RP, at 3 years following treatment 68% of men reported being unable to achieve an erection satisfactory for intercourse, compared with 36% of men who were treated with LDRBT.

In one study no difference was reported between potency rates following treatment with either EBRT or LDRBT. Another study that did report a difference in potency rates was biased by patient selection and use of phosphodiesterase-5 (PDE-5) inhibitors, making interpretation difficult.

One study reported on potency rates among men managed with AS; however, a proportion of men were treated with EBRT, LDRBT or RP in the follow-up period and this will impact on the potency rates.

Health-related quality of life

At times shortly following treatment, quality of life (QoL) is likely to be affected by the side effects of that treatment. Studies reporting on comparative health-related QoL showed mixed results, although those with longer follow-up times frequently showed no difference between groups, or reported on small differences that are unlikely to be clinically meaningful or noticeable to the patient.

Within 6 months following treatment, LDRBT consistently performed better than RP, which is likely to be due to the immediate nature of RP side effects compared with the delayed onset of some LDRBT side effects. Differences did not extend beyond 6 months or, in two studies, better QoL was reported among RP patients. Reported differences in QoL between men treated with LDRBT and RP were small.

Little difference in QoL was reported by studies (which reported mixed results) among men treated with EBRT compared with men treated with LDRBT. Among studies correcting for baseline QoL, there was no difference following LDRBT and EBRT.

QoL among men managed with AS was reported by one study and was no different from LDRBT at 3 years following treatment.

Key uncertainties

With the exception of one randomised controlled trial, all other included comparative studies (n=16) were cohort or matched single-arm studies. Some results have been presented following adjustment for baseline characteristics and some studies have matched patients on characteristics important for the prognosis of prostate cancer; however, no study has matched patients a priori on urinary, bowel or sexual function. The lack of homogeneity regarding function at baseline and the possible effect of patient selection (into a treatment that will provide the best possible individual outcome in terms of side effects) markedly affects the uncertainty surrounding the comparative safety of treatments.

Importantly, the age of men receiving different treatments often differs substantially. Therefore, baseline characteristics (urinary, bowel and sexual function) and the propensity to be harmed by treatment may differ between treatment arms at the outset. This will be particularly true for sexual dysfunction following treatment because normal erectile function declines rapidly in men from their seventh decade onward. While erectile function may appear to be worse following one treatment, it is possible that this is an artefact of an ageing treatment group whose erectile function may have declined irrespective of the intervention.

When reporting urinary incontinence, no distinction is made between possible causes of the incontinence, which is likely to be different between surgery- and radiation-based treatments. The nature of urinary incontinence (lack of control post surgery, obstructive or overflow incontinence or irritative/urge) is important information as patients may wish to avoid particular treatments that result in a type of incontinence that they are most prone to.

When comparing studies involving EBRT and LDRBT, considerable inconsistency exists. Whether this is a reflection of differences in treatment practice or an effect of the different methods or tools used to measure side effects, it is likely that the differences in safety outcomes of the two modalities are largely similar.

A lack of studies comparing outcomes following LDRBT and AS makes conclusions about the relative safety of AS compared with LDRBT difficult.

Overall conclusion with respect to comparative safety

Urinary symptoms are common following LDRBT, EBRT and RP for localised prostate cancer. Men receiving LDRBT or EBRT are more likely to report irritative or obstructive urinary symptoms than men treated with RP. Irritative and obstructive symptoms abate with time and no difference between the treatments is reported at 5 years. Urinary incontinence is more common immediately following RP compared with LDRBT (68% compared with 17%). Although incontinence remains more common in men following RP at 3 years than LDRBT or EBRT, the differences between the treatments are more modest. Urinary retention is more common following treatment with LDRBT than with RP and more common following LDRBT than EBRT, although each of these findings is based on single comparative studies.

Rectal bleeding is more common, and faecal incontinence may be more common, following LDRBT than RP; however, these assertions are based on only two studies. Bowel side effects may be fewer following LDRBT than EBRT, with most studies using bowel-specific questionnaires reporting higher bother or worse function among EBRT patients than LDRBT patients.

Erectile dysfunction is more common following RP than LDRBT and is unlikely to be different between LDRBT and EBRT.

Insufficient evidence of AS was available to draw definitive conclusions regarding its comparative safety.

Effectiveness

A total of six comparative studies reported on the primary or secondary effectiveness of low-dose-rate brachytherapy (LDRBT) compared with external beam radiotherapy (EBRT) or radical prostatectomy (RP). No studies were identified comparing active surveillance (AS) with LDRBT.

Key results

Primary effectiveness

In a study examining death from any cause, actuarial 7-year survival was reported as 82% for LDRBT, 72% for EBRT and 89% for RP. When adjusted for baseline characteristics (such as known prognostic indicators for prostate cancer, age and comorbidities), survival following LDRBT and RP was no different, although both were significantly greater than survival following EBRT.

The same study reported on prostate cancer specific survival and showed little difference between the treatment arms (97% survival for LDRBT, 94% for EBRT and 98% for RP). This study was unable to adjust for PSA levels. Due to likely patterns of patient selection, PSA levels would be expected to be lower in men treated with LDRBT and highest among men treated with EBRT, and this may explain the small differences in prostate cancer specific survival between the groups.

As the differences in overall survival among men treated with LDRBT and EBRT are unexplained by excess prostate cancer deaths, it is likely that they are a result of unknown or uncontrolled-for confounders rather than a true difference in treatment effectiveness.

Secondary effectiveness

Five-year freedom from biochemical recurrence (bNED) was reported by one randomised controlled trial and found to be 91.7% and 91% among men randomised to LDRBT and RP respectively. However, the definition used to calculate biochemical recurrence was not reported and, as definitions differ between surgical and radiotherapy modalities, it is uncertain whether bias may have been introduced by systematic differences in the sensitivity or specificity of the definitions used. No other study compared LDRBT with RP.

Studies that compared LDRBT with EBRT in terms of bNED tended to find no difference. One study showed improved outcomes following LDRBT compared with EBRT; however, a large proportion of men treated with EBRT in this study were inadequately dosed.

Key uncertainties

With the exception of one randomised controlled trial involving LDRBT and RP, studies were not randomised and confounding cannot be ruled out. Men receiving EBRT tend to have higher risk disease and more comorbidities than men undergoing either LDRBT or RP; therefore, differences in survival may be confounded by patient selection.

Due to the prolonged natural history of prostate cancer, often requiring more than 15 years from diagnosis to death, studies reporting on outcomes of less than 10 years may

not be sufficiently long to show meaningful differences (if they exist) between treatments. One method used to forecast future outcomes is to use shorter term proxy or surrogate outcomes, such as bNED. However, the sensitivity and specificity of biochemical recurrence for predicting meaningful clinical outcomes such as time to metastases or death are poorly understood. In particular, differences in definitions of biochemical recurrence, necessitated by the different effects of surgery compared with radiation-based therapies on PSA, may have quite disparate abilities to predict the onset of clinically important events. Therefore, the direct comparison of bNED between surgery and radiation therapies may also be fraught with unknown confounders.

Overall conclusion with respect to comparative effectiveness

Men who receive LDRBT or RP have better overall survival than men who receive EBRT; however, this is unlikely to be due to differences in treatment effectiveness and more likely to be due to confounders resulting from patient selection. Disease-specific survival across all treatments is likely to be the same.

Five-year freedom from biochemical recurrence following LDRBT and RP is similar. Among men who receive LDRBT and men treated with EBRT (with present day prescriptions), 5- and 7-year bNED are similar.

Other relevant considerations

In 2007, without a systematic assessment process, the eligibility criteria for Medicare reimbursement for LDRBT were expanded to include men diagnosed with Gleason 7 disease. The expert opinion of the Advisory Panel, in agreement with a growing body of evidence, was that men diagnosed with Gleason score 7, whose primary Gleason grade is 4 (4+3 = 7) are at a higher risk of poor oncological outcomes compared with men whose primary Gleason grade is 3 (3+4 = 7). Therefore, it was the intent of this current review to assess separately the safety, effectiveness and cost-effectiveness of LDRBT for men diagnosed with: Gleason 6 prostate cancer; Gleason 7 prostate cancer predominantly made up of Gleason grade 3; and Gleason 7 prostate cancer predominantly made up of Gleason grade 4.

No studies were identified that stratified men into these Gleason groups, or they did so but rendered the Gleason 7 groups ineligible for this review due to the inclusion of patients with other higher risk factors (ie PSA > 10 ng/mL).

Despite the absence of evidence found by this review, the Advisory Panel has reservations about endorsing the use of LDRBT for treating men diagnosed with Gleason 4+3 = 7 disease due to the higher likelihood of extracapsular extension in this group and the lack of international guidelines supporting treatment of Gleason 4+3 = 7 with LDRBT as monotherapy (in the absence of adjuvant EBRT).

Economic evaluation

Three costing studies (one based in France and two in the US) reported on the comparative costs of low-dose-rate brachytherapy (LDRBT) and radical prostatectomy (RP). Two studies reported that costs associated with LDRBT and RP were similar, and one study reported that costs associated with LDRBT were substantially greater. Due to

the differences in healthcare systems, it is unclear how applicable these results are to the Australian healthcare setting.

One health technology assessment (HTA) based in the US combined the results from three systematic reviews of LDRBT; RP and active surveillance (AS); and intensity modulated radiotherapy (IMRT), a form of external beam radiotherapy (EBRT). Under the assumption of equivalent effectiveness and varying only costs and patient utility resulting from treatment side effects, LDRBT was reported to result in 0.3 more quality adjusted life years (QALYs) compared with RP. LDRBT was also reported to be less expensive than RP. Compared with RP, IMRT provided 0.27 more QALYs although at a higher cost, resulting in an incremental cost-effectiveness ratio (ICER) of $35,233. AS resulted in 1.15 more QALYs than RP at an ICER of $1,803.

Financial impact analysis

It is estimated that 5,000 men will be diagnosed with localised prostate cancer and would be eligible for treatment with LDRBT in 2010. The anticipated uptake of LDRBT is 1,400 in 2010, but this is likely to increase.

The differences in overall costs of each of the treatments are small. Including all non-trivial costs over 1 year, but excluding the cost of disease recurrence (assumed to be identical across all three treatments) and of managing treatment side effects, the cost of treating one man with LDRBT will be $12,950 if he has Gleason ≤ 6 disease and $13,800 if he has Gleason 7 disease. The increased cost associated with Gleason 7 prostate cancer reflects the additional staging scans required following initial diagnosis. Assuming that 55% of men who are eligible for LDRBT have Gleason ≤ 6 prostate cancer, the average cost of LDRBT is $13,322 per patient. The average cost of treating one man with EBRT is $13,428, and to treat one man with RP will cost $13,286.

The annual cost to the MBS of treating one-third of the 5,000 potentially eligible men with LDRBT, one-third with EBRT and one-third with RP would be $28.362 million. The cost to the MBS of providing LDRBT is substantially less than for EBRT, but this cost saving is entirely attributable to the redistribution of costs to other sectors of the Australian healthcare system.

Overall annual costs to the Australian healthcare system for treating one-third of the 5,000 potentially eligible men with LDRBT, one-third with EBRT and one-third with RP is $66.727 million. As the overall costs of providing LDRBT are similar to those for EBRT and RP, and men are equally likely to be drawn from each of these competing treatments, the financial impact of continued listing of LDRBT on the MBS is minimal.

The cost of providing AS is largely contingent upon the number of men who opt for, and persist with, this treatment. AS may be inappropriate for men with Gleason 7 prostate cancer, and therefore it has been costed only for men with Gleason ≤ 6 disease. The best estimate for the use of AS in this population in Australia is 20%. Assuming that 57% of men who select AS will proceed to active treatment over 10 years, the discounted annual cost of treating 5,000 men with LDRBT, RP, EBRT or AS is estimated at $65.684 million. If the uptake of AS increases, or the transition to active treatment decreases, the overall cost of managing 5,000 men with localised prostate cancer will be reduced.

Introduction

Adelaide Health Technology Assessment, with input and advice from an appropriately constituted Advisory Panel of experts (see Appendix B), has reviewed the use of low-dose-rate (LDR) permanent seed brachytherapy (BT) for the treatment of early localised prostate cancer.

This assessment report is intended for the Medical Services Advisory Committee (MSAC). The MSAC evaluates new and existing health technologies and procedures for which public funding is sought in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. The MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

This report summarises the assessment of current evidence on LDR permanent seed BT for the treatment of early localised prostate cancer. It updates and expands upon two previous MSAC assessments (Medical Services Advisory Committee 2000 and Medical Services Advisory Committee 2005).

Rationale for assessment

This review of Application 1089 is a reference from the Australian Department of Health and Ageing to the MSAC to have an assessment undertaken of the safety, effectiveness and cost-effectiveness of LDR ^{125}I BT for the treatment of localised prostate cancer. The MSAC assessment (1089) in 2005 recommended continued interim public funding for LDRBT for the treatment of prostate cancer. The Minister for Health and Ageing accepted this recommendation on 28 November 2005. This current assessment updates the previous two MSAC assessments published in 2000 and 2005, so that the interim funding recommendation can be reviewed.

Background

Previous MSAC assessments

Initial MSAC assessment 1029

The initial MSAC review of the safety, effectiveness and cost-effectiveness of iodine-125 (^{125}I) LDRBT for prostate cancer was undertaken in 2000 (MSAC application number 1029). This review compared LDRBT as a treatment for early, localised prostate cancer with those treatments then in use in Australia: radical prostatectomy (RP), external beam radiotherapy (EBRT) and active surveillance (AS). The assessment was unable to identify any randomised controlled trials (RCTs) comparing the effectiveness of treatments, and conclusions were therefore based on level III and level IV evidence.

The recommendation for interim funding for men with localised prostate cancer, with Gleason scores of 6 or less and with a prostate specific antigen (PSA) of 10 ng/mL or less, was accepted by the Minister for Health and Aged Care on 9 February 2001.

MSAC review 1089

In 2005 the MSAC re-reviewed LDR ^{125}I BT as a treatment for early, localised prostate cancer incorporating new evidence generated since the initial review. The evidence available for this review was not strong (level III) and the lack of RCTs precluded substantive conclusions regarding the safety and effectiveness of LDRBT in comparison with RP, EBRT or AS. The report found that there was no evidence available that demonstrated a difference in survival or disease progression between LDRBT, RP and EBRT. Furthermore, there were no studies directly comparing either survival or disease progression in men treated with LDRBT or AS. Low-level evidence (level III-2) suggested that LDRBT may be comparable to, or better than, RP or EBRT in terms of sexual functioning following treatment, as well as resulting in lower rates of post-treatment incontinence. It was reported that LDRBT may result in higher rates of lower urinary tract (irritative or obstructive) symptoms than EBRT, and higher or comparable rates of rectal side effects compared with EBRT based on a small number of included studies. Faecal incontinence was potentially higher in patients treated with LDRBT compared with those treated with RP. Limited evidence (level III-2) reported that overall quality of life at 1 year post treatment was comparable for LDRBT and RP.

Direct costs of LDRBT compared with RP and EBRT, were estimated using current Australian pricing of staff, procedures and materials required for each treatment option. The adverse event rates and associated utilities, modelled into quality adjusted life years (QALYs), were taken from a cost-effectiveness model (Hummel et al 2003) generated on behalf of the National Institute for Health and Clinical Excellence (NICE). Incremental QALYs for LDRBT versus AS were small, estimated at 0.55 compared with 0.26 for RP and –0.05 for EBRT. These were based on the assumption of equivalent patient survival. However, LDRBT was more costly than either RP or EBRT. Incremental cost effectiveness ratios (ICERs—cost per QALY) were not reported due to the variability of the ICER estimates in the sensitivity analyses.

These findings, in combination with the findings of the initial MSAC assessment, led to the MSAC's recommendation to continue interim funding at approved sites for LDRBT in the treatment of men with early localised prostate cancer. This recommendation was accepted by the Minister for Health and Ageing in 2005.

MBS amendment July 2007

In 2006 an application was submitted to the Department of Health and Ageing by the Australian and New Zealand Association of Urological Surgeons (ANZAUS) citing studies supporting the expansion of the eligibility criteria for LDRBT to include patients with a prostate cancer Gleason score of 7. No other alteration to the eligibility criteria was sought. Primarily, the argument for including patients with Gleason scores of 7 on biopsy related to the upward migration of Gleason scores in recent times, such that a proportion of Gleason 6 patients considered by earlier MSAC reviews would, were they regraded in 2006, be scored as Gleason 7 (which would render them ineligible for LDRBT).

The NHMRC Clinical Trials Centre (CTC) undertook a critique of the evidence presented in the ANZAUS submission, and found a consistent pattern supporting the change in histopathological scoring of prostate cancer resulting in an increased assignment to Gleason 7. It was concluded that the studies reviewed supported the proposal for increasing the Gleason score cut-off for LDRBT to 7. This recommendation was accepted by the Minister for Health and Ageing, and the criteria for MBS item numbers 37220 and 15338 were amended in July 2007 (Medicare Australia 2007).

However, the evidence presented by ANZAUS was non-systematically obtained and the assessment by CTC was not considered to be equivalent to a full systematic review. An evidence-based decision regarding this subpopulation is particularly important as it is likely to result in a substantial increase in the proportion of patients eligible for Medicare reimbursement for LDRBT in Australia.

This review will consider evidence published since 2005 and update the findings of the previous two MSAC assessments (1029 and 1089) for the patient cohort described before the change in reimbursement criteria (ie Gleason score ≤ 6). In addition, this review will consider all evidence from 2000 for the subpopulation that was excluded from previous MSAC assessments but have been eligible for MBS-funded LDRBT since 2007 (ie Gleason score = 7).

Brachytherapy

The procedure

LDRBT (also known as permanent interstitial radiotherapy or seed BT) is the implantation of radioisotopes (iodine-125 or palladium-103) directly into the prostate gland. The implantation is carried out under transrectal ultrasound guidance and can be performed as a day-patient procedure, although it usually involves at least an overnight stay. The radioactive sources are distributed throughout the prostate according to planning done pre- or intra-operatively to ensure adequate coverage of radiation (emitted as X- and gamma rays) for the ablation of tumour cells. BT seeds have a local effect, with

a sharp dose fall-off, governed by the inverse square law, resulting in adjacent tissues receiving only very low doses of radiation.

LDRBT is performed using either palladium-103- (^{103}Pd) or iodine-125- (^{125}I) filled titanium seeds. While ^{125}I and ^{103}Pd decay at different rates, there is insufficient evidence to show that the isotopes result in different patient outcomes. However, this remains a possibility and, as only ^{125}I seeds are available in Australia, data from studies using ^{103}Pd have not been considered in this review. Seeds may be delivered as single units or attached by absorbable sutures in strands. Some studies have shown that stranded seeds have a lower incidence of seed loss or migration to structures outside the prostate (Al-Qaisieh et al 2004; Reed et al 2007).

LDRBT in Australia is delivered via the perineal percutaneous route. Historically, ^{125}I seeds were placed using a retropubic approach (Carlton et al 1972; Whitmore et al 1972), often accompanied by pelvic lymph node dissection, which was associated with poorer outcomes (Fowler et al 1979; Zelefsky & Whitmore 1997). Only current methods of relevance to practice in Australia will be considered as part of this review.

Iodine-125 has a half-life of 60 days, and decays to tellurium-125 via an excited state of tellurium-125, emitting photons of various energies as well as Auger electrons. The most abundant photon emission is a 27 keV X-ray. Each seed typically has an activity of 11–15 MBq (0.3–0.4 mCi), and seeds are distributed to achieve a prescribed dose of 145 Gy to the planning volume. Post-implant dosimetry is performed by imaging of the prostate and the ^{125}I seeds to confirm adequate coverage, and that an acceptable dose has been delivered to the planned region. An excellent dose distribution occurs when the proportion of the prostate that receives the full prescribed dose nears 100% without adjacent structures receiving unacceptably high doses of radiation. Currently, the total radiation dose to the prostate from LDRBT (145 Gy) is numerically about twice that from conventional EBRT (typically 70–80 Gy), with a somewhat greater biologically effective dose to tumour and prostate tissue (Lehnert et al 2005), and lower doses to surrounding tissue.

Whether prostate size or pubic arch interference are contraindications to LDRBT is uncertain, and has been refuted by Merrick and Wallner et al (2004) and the American Brachytherapy Society (Merrick et al 2004; Nag et al 1999). However, large prostates are reported as a relative contraindication, with the best results attained only from experienced brachytherapists. LDRBT may be given to individuals with large prostates if a short (3–6 months) course of adjuvant androgen deprivation therapy, usually luteinising hormone-releasing hormone (LHRH) agonists, is administered. This acts to decrease the tumour and prostate volume to a more acceptable range. In higher risk patients, LDRBT may be combined with EBRT; however, only LDRBT as a monotherapy is being assessed in this review.

The LDRBT procedure involves a urologist, radiation oncologist, medical physicist, radiation therapist and anaesthetist. Sophisticated planning software and imaging technology are required for the implantation and post-implant dosimetry. Implants that are found to have inadequately dosed the prostate in some areas may be 'topped up' with further seeds, requiring a second procedure or using subsequent EBRT (Stock & Stone 2002).

LDRBT is proposed to be an efficient, effective and safe treatment for men with early, localised prostate cancer. The in-hospital duration (1–2 days) is shorter than the usual

EBRT outpatient daily regimen of 7+ weeks. Survival following LDRBT is considered by some to be equivalent to EBRT and RP, with a different adverse event profile more acceptable to some patients (ie potentially with lower rates of erectile dysfunction and incontinence than RP). However, according to the previous MSAC assessment (1089), LDRBT is currently more expensive and may be associated with different complications. The proposed benefits and costs are investigated further in subsequent sections of this assessment.

Intended purpose

LDRBT as a monotherapy is intended for use in the treatment of early localised prostate cancer. Current Australian clinical practice guidelines for the management of localised prostate cancer (Australian Cancer Network Working Party 2002) recommend LDRBT for patients with 'localised prostate cancer of low volume with Gleason score < 7 and greater than a 10-year life expectancy'. This recommendation was reinforced in the previous 2005 MSAC review (1089). The MSAC's indications for the use of LDRBT following the 2005 review are listed below:

- clinical stages T1 and T2
- Gleason score ≤ 6
- prostate specific antigen ≤ 10 ng/mL
- prostate gland volume less than 40 cc
- life expectancy ≥ 10 years.

In July 2007 eligibility criteria for medical benefits reimbursement were amended to include patients with Gleason scores of 7.

These indications are similar to those recommended by most international agencies (American Brachytherapy Society (ABS) 2007; American Urological Association (AUA) 2007; European Association of Urology (EAU) 2009; National Comprehensive Cancer Network (NCCN) 2010; National Institute for Health and Clinical Excellence (NICE) 2008), as presented in Table 1.

Table 1 Indications for low-dose-rate brachytherapy according to international guidelines

Indications	EAU[a]	AUA[b]	NCCN[c]	NICE[d]	ABS[e]
Clinical stage	T1b–T2a	T1c–T2a	T1–T2a	T1–T2c	T1b–T2b
Gleason score	≤ 6 (or 3+4)[f]	≤ 6	≤ 6	≤ 7	≤ 6
Prostate specific antigen (PSA)	≤ 10 ng/mL	≤ 10 ng/mL	< 10 ng/mL	< 20 ng/mL	≤ 10 ng/mL
Gland volume	< 50 cc	-	-	-	-
Life expectancy	> 10 years[g]	-	≥ 10 years	-	> 5 years
IPSS	Good (0–8)	-	-	-	-
Dose (^{125}I)	145 Gy	-	145 Gy	-	145 Gy
Other	No previous TURP[h] < 50% biopsy cores positive		Large and very small prostates or poor IPSS[i] are contra-indicated		Evidence of N or M disease[j], inflammatory bowel disease and extensive TURP defects are contra-indicated

[a] European Association of Urology (EAU); [b] American Urological Association; [c] National Comprehensive Cancer Network; [d] National Institute for Health and Clinical Excellence; [e] American Brachytherapy Society; [f] The appropriateness of brachytherapy for Gleason 3+4 is presented as uncertain in the EAU guidelines; [g] a condition for all definitive therapy in these guidelines and not explicitly stated as a condition of brachytherapy; [h] transurethral resection of the prostate; [i] International Prostate Symptoms Score; [j] nodal (N) or metastatic (M) disease

Defining the target population

Staging and grading of prostate cancer is central to disease prognosis and therefore treatment choice. Strategies for determining the stage, grade and likelihood of the presence of adverse features of prostate cancer are discussed below. This evaluation of LDRBT is restricted to patients with localised (stages T1–2), well to moderately differentiated (Gleason ≤ 7) cancer with a PSA ≤ 10 ng/mL.

Tumour–nodes–metastases staging

The tumour–nodes–metastases (TNM) staging system describes the extent of tumour in a patient's body. The tumour (T) staging describes the size of the tumour and whether it has invaded adjacent structures; the nodal (N) staging describes the involvement of regional lymph nodes; the metastases (M) staging describes distant spread of the tumour, such as to other organs or bone. The TNM staging system is managed by the International Union Against Cancer (UICC—Union Internationale Contre le Cancer) and is a globally recognised method for describing the extent of cancers. The most recent edition was released in 2009 (Sobin et al 2009), and an explanation of this staging system is presented in Table 2.

In prostate cancer, tumour staging is a clinical judgement based on the digital rectal exam and available imaging, such as ultrasound or magnetic resonance imaging (MRI). Nodal staging is assessed by means of computerised tomography (CT) or MRI scan. Prostate cancer guidelines usually recommend against the use of CT scans in the staging of men with low-risk prostate cancer; however, these scans may be used in the course of LDRBT

for planning purposes (Krempien et al 2003). Staging of skeletal metastases is assessed by whole-body radionuclide bone scanning although, once again, bone scans may not be warranted in patients deemed to be at low risk (American Urological Association (AUA) 2007; European Association of Urology (EAU) 2009; National Institute for Health and Clinical Excellence (NICE) 2008).

Table 2 UICC[a] tumour–nodes–metastasis staging system for prostate cancer

Classification	Definition
T classification	**Primary tumour**
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour, not detected by digital rectal examination or visible by imaging
T1a	Incidental histological finding; ≤ 5% of tissue resected during TURP
T1b	Incidental histological finding; > 5% of tissue resected during TURP
T1c	Tumour identified by needle biopsy
T2	Tumour confined within the prostate
T2a	Tumour involves half of one lobe or less
T2b	Tumour involves more than half of one lobe but not both lobes
T2c	Tumour involves both lobes
T3	Tumour extends through the prostate capsule but has not spread to other organs
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles
N classification	**Regional lymph nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M classification	**Distant metastases**
M0	No distant metastases
M1	Distant metastases

[a] Sobin et al (eds) 2009

Gleason score

The Gleason score is a histopathological system used for grading the degree of differentiation of prostate cancer cells. The score is made up of the sum of two scores—the first representing the grade of the most prevalent tumour cells and the second the grade of the next most prevalent tumour cells (comprising at least 5% of the tumour examined). Each tumour score is out of 5, with 1 being well differentiated and 5 being undifferentiated, thus giving a possible minimum score of 2 and a possible maximum score of 10. As a prognostic variable, Gleason scores of less than 7 are usually deemed low risk, 7 are intermediate risk, and greater than 7 are high risk in the absence of other adverse prognostic factors.

Good evidence suggests that patients with a Gleason score of 7 but with a preponderance of Gleason grade 3 (ie 3+4 = 7) experience better prognoses than those with a preponderance of Gleason grade 4 (ie 4+3 = 7) (Chan et al 2000; Kang et al 2007; Khoddami et al 2004; Lau et al 2001; Makarov et al 2002; Rasiah et al 2003). Importantly, tumours with Gleason scores of 4+3 = 7 may behave more like tumours with scores of

4+4 = 8 than tumours with scores of 3+4 = 7 (Kang et al 2007). In addition, 4+3 = 7 tumours, which are clinically inapparent with PSA 6.1–10.0 ng/mL, remain organ confined in only 43 % of cases [95% CI: 35-51], compared with 54% of cases [95% CI: 49-59] for 3+4 = 7 tumours (Partin et al 2001).

The differences in risk and likelihood of spread beyond the prostate for Gleason scores 3+4 and 4+3 may have important ramifications for the appropriateness of prostate cancer treatments. LDRBT, in particular, is a localised treatment with little effect beyond the prostate due to the rapid dose fall-off from the BT seeds.

Prostate-specific-antigen (PSA)

PSA is a protein produced by the prostate that is present in the blood. Many different processes in the prostate may lead to a raised PSA level (eg infection, benign hypertrophy or cancer), but it has long been used as a marker for the presence of prostate cancer (Aus et al 2005; Gann et al 1995; Stenman et al 1994), a predictor of tumour stage (Pinsky et al 2007; Stamey et al 1987) and a prognostic marker for patient outcomes, as shown by its use in almost all prostate cancer risk assessment tools (Cooperberg et al 2005; D'Amico et al 2007; Kattan et al 1998; Stephenson et al 2005).

As PSA testing becomes more widespread and patients are diagnosed with earlier stage and possibly clinically irrelevant cancer, PSA may become a less important predictor of adverse pathological findings (Stamey et al 2004). This trend, however, has had little effect on the use of PSA to classify risk, and it remains an important marker of nodal or distant disease at higher levels (Catalona & Loeb 2005).

Contraindications

LDRBT is contraindicated in those patients:

- with a history of extensive transurethral resection of the prostate (TURP)

The American Brachytherapy Society states that a large TURP defect can be technically difficult to plan and results in a heightened chance of loss of seeds, and that patients may be at a greater risk of harmful outcomes (Nag et al 1999).

- who have pre-treatment obstructive urinary symptoms

The European Association of Urology recommends against using LDRBT in patients with an International Prostate Symptoms Score (IPSS)[1] of ≥ 8 (Ash et al 2000), as these patients may be at greater risk of obstruction following the procedure.

- with prostates larger than 50 cc

Large prostates may be difficult to access via the perineal route and be associated with higher rates of urinary retention following seed implantation (Ash et al 2000). Adjuvant androgen deprivation therapy (ADT) may be used to reduce the prostate to a more appropriate size; however, the harms associated with ADT should be considered.

[1] IPSS measures irritative and obstructive urinary symptoms such as incomplete emptying, urinary frequency, intermittency, urgency, weak stream, straining and nocturia.

- with intermediate- or high-risk prostate cancer

Definitions of intermediate-risk prostate cancer vary, although it usually includes men with a Gleason score ≥ 7 or PSA > 10 ng/mL or clinical stage T2b–c (D'Amico et al 1998; National Comprehensive Cancer Network (NCCN) 2010). The National Institute for Health and Clinical Excellence (NICE) guideline for prostate cancer (2008) is the only current guideline that does not specifically advise against LDRBT (delivered as monotherapy) for patients with intermediate-risk prostate cancer (see Table 1). However, the NICE guidelines appear to be for both LDRBT delivered as monotherapy and with an EBRT boost. Therefore, with the exception of the NICE guideline for prostate cancer, the Australian reimbursement for LDRBT as monotherapy for patients with intermediate-risk prostate cancer (Gleason 7 disease and clinical stage T2c) appears unique.

Follow-up

Follow-up or monitoring after treatment for localised prostate cancer is primarily used to identify and treat complications of radical treatment, identify early disease progression for which further adjuvant or salvage therapy may still be effective, and audit the outcomes of treatment (National Institute for Health and Clinical Excellence (NICE) 2008). Follow-up should continue for at least 2 years, and men who have no ongoing significant treatment complications should be offered follow-up in primary care or via telephone. PSA levels should be recorded at least 6-monthly for 2 years, and at least yearly thereafter (National Institute for Health and Clinical Excellence (NICE) 2008).

PSA monitoring following radical treatment may help provide an indication of treatment failure. If treatment failure is identified early, additional radical treatment may be prescribed. However, further treatment based solely on PSA-assessed recurrence is of questionable merit (McLeod 2005). The use of a post-treatment PSA increase (biochemical recurrence (BR)) by investigators as a surrogate outcome for survival or cancer progression is common, although is fraught with problems (Kuban et al 2004). Definitions of BR vary across and within treatments, and across time periods. Recently, BR following radiotherapy has been defined as a rise of 2 ng/mL above the nadir[2] (Abramowitz et al 2008) and has replaced the previous American Society for Therapeutic Radiology and Oncology (ASTRO) definition that required three consecutive rises[3]. The newer definition has been shown to be a better surrogate for disease progression, overall survival and disease-specific survival (Kuban et al 2006; Roach et al 2006). However, there has been some criticism of the false positive identification of BR in men who receive LDRBT (Thompson et al 2010). In addition, BR lacks specificity and so a far greater number of men experience treatment failure according to PSA measures than do men who progress or die of prostate cancer (Jhaveri et al 1999; Pound et al 1999). Given that BR is measured differently in men who undergo RP, and is impossible to interpret in men who select AS, BR may be a poor surrogate measure for treatment effectiveness, particularly when comparing modalities. A more accurate measure would be disease-specific or all-cause survival. The drawback of not having an appropriate surrogate marker for survival in men with early localised prostate cancer is that the disease can be

[2] Commonly referenced as the 'Phoenix' definition.
[3] Commonly referenced as the 'ASTRO' definition.

indolent or very slow to progress. Pound et al (1999) reported that the median time to metastatic disease following BR was 8 years, although this was closer to 10 years in men with Gleason scores < 7. It was then a median of 5 years from the development of metastases to death. As such, expensive long-term trials are required to study the outcomes of treatments for low-risk prostate cancer patients, and often technologies alter before definitive results are available. LDRBT in its current form has not been available for sufficiently long to generate meaningful survival evidence.

Assessment of adverse events

All accepted forms of treatment for prostate cancer involve side effects. However, the nature and severity of side effects may differ from treatment to treatment, and the tools used to measure side effects also vary. The American Brachytherapy Society recommends that studies of LDRBT use the IPSS, the International Index of Erectile Function (IIEF) and the Radiation Therapy Oncology Group (RTOG) toxicity grading criteria to record urinary, sexual and bowel symptoms respectively. Unfortunately, the IPSS records irritative or obstructive urinary symptoms, which are common in radiotherapy modalities, yet does not record incontinence or urinary control, which is a far greater complaint following RP. This results in difficulties when comparing patient outcomes across modalities. In addition, the tools are often used to report symptoms at a defined time following treatment with little regard for pre-treatment morbidity. This can be problematic, particularly as the population who tend to be diagnosed with prostate cancer also tend to be older and therefore have a higher rate of baseline (pre-treatment) urinary, sexual or bowel symptoms.

Comparisons between treatments with disparate side effect profiles, such as LDRBT and RP, are complicated by differences in consumer preference. Patients may accept an increased risk of some adverse events if a treatment minimises the risk of less desirable adverse events, although which side effects are less desirable will be specific to the patient. Therefore, measures that convert certain health states, such as erectile dysfunction or urinary incontinence, to broad metrics such as QALYs can only do so by accepting a mean measure, and may inadequately reflect the importance of certain health states (or avoiding certain health states) in individuals.

Clinical need / burden of disease

Natural history of early localised prostate cancer

Prostate cancer is a heterogeneous disease encompassing a continuum of clinical outcomes. Some patients will experience rapid disease progression, while others may live with prostate cancer for many years only to die of an unrelated illness. Figures from Australia estimate that as many as one in five men will be diagnosed with prostate cancer by the age of 85 years, yet it will account for only about 4% of all male deaths (Australian Institute of Health and Welfare (AIHW) 2009a).

A population-based cohort study of men in Sweden that studied 223 patients diagnosed with localised prostate cancer who were treated conservatively reported consistently low mortality rates (average 15/1,000 person years) until 15 years following diagnosis (Johansson et al 2004). This represents a disease-specific survival for all patients of nearly

80%. At the same time point, overall survival was marginally greater than 20%, a reflection that the vast majority of men had died of unrelated causes. The authors report a decrease in disease-specific survival over the following 5 years to 54.5%; however, this change is based on very small numbers (8 deaths from prostate cancer). This study highlights that early localised prostate cancer follows, in most cases, an indolent course, requiring many years before death due to prostate cancer. It is important to note that the Johansson study recruited patients from 1977 until 1984, a period that pre-dates the use of PSA testing, which has subsequently altered prostate cancer detection rates and time to event analyses. In addition, all cancer grades were included, and many of the prostate cancer deaths were among men with higher grade cancers.

With the advent of PSA testing, the proportion of men who are diagnosed with prostate cancer has risen sharply, reflecting an increased diagnosis of clinically irrelevant cancers. In addition, PSA testing has introduced, in many men, a lead time of about 10 years (Draisma et al 2003) before symptoms or clinical examination may have led to a diagnosis, therefore complicating comparisons of survival between historical (pre-PSA) studies and contemporary studies, and between studies from countries with disparate rates of PSA testing.

At present it is not possible to differentiate clinically irrelevant cancers from those that will progress to cause morbidity or death. Draisma et al (2003) estimated that, with the advent of PSA screening, detection of clinically insignificant cancers may be as high as 50%. Until a useful marker is discovered to identify those patients who will benefit from treatment, it is important to ensure that any treatment given (particularly in patients with low-risk tumours) balances the low likelihood of progression and death with the potential for adverse events and changes in quality of life imposed by the treatment.

Epidemiology

Incidence and mortality rates

Prostate cancer is the most commonly diagnosed cancer in Australian men (excluding non-melanocytic skin cancer) and the most common cancer diagnosed in Australians overall (men and women), followed by colorectal cancer and breast cancer. Prostate cancer is the second leading cause of cancer deaths in men after lung cancer (Australian Institute of Health and Welfare (AIHW) & Australasian Association of Cancer Registries (AACR) 2008).

In 2006 there were 17,444 new cases of prostate cancer and 2,971 deaths attributed to prostate cancer among Australian men (Australian Institute of Health and Welfare (AIHW) 2009a). These numbers represent 29.5% of all male cancers and 13.3% of all male cancer deaths for 2006. The incidence rate has been steadily rising in Australia since 2000 following a decline from its peak in 1994 of 184.3 per 100,000 males (age standardised to the Australian Standard Population 2001). The sudden increase of diagnoses in Australia in the early to mid 1990s most likely reflects the introduction of PSA testing and mirrors a trend that occurred in the US about 3 years earlier. In 2006 the age-standardised incidence rate for prostate cancer in Australian men reached 170.0 per 100,000 males.

Despite increases in incidence, cancer-specific mortality has fallen to 31.0 deaths per 100,000 Australian men in 2007 from more than 40 per 100,000 in the mid 1990s. This may reflect the benefits of earlier detection, effective radical treatment and life-prolonging

interventions such as ADT. The high death rates in the mid 1990s may also be due to bias related to the misattribution of cause of death (Collin et al 2008). The 5-year relative survival rate of men with prostate cancer has increased from 57% in the period 1982–86 to 85% in 1998–2004 (Australian Institute of Health and Welfare 2008). However, this trend is probably the result of over-diagnosis and the introduction of lead time bias due to the use of PSA testing. Irrespective of the degree of over-diagnosis of prostate cancer, absolute numbers of men dying from the disease outnumber deaths due to breast cancer.

With the advent of PSA testing, the average age at diagnosis of prostate cancer has fallen from 73 years in 1982 to 69 years in 2006; however, it remains a very rare disease in men younger than 50 years of age. The lifetime risk of developing prostate cancer before the age of 75 years now stands at about one in seven; by the age of 85 years, it is expected that one in every five men will have a prostate cancer diagnosis.

While age at diagnosis continues to fall, prostate cancer mortality continues to occur later in life, with an average age at death of 78.6 years in 2006. Consequently, despite its prevalence, prostate cancer has a lower overall burden of disease when measured by potential years of life lost (PYLL) compared with other cancers. In 2006 prostate cancer resulted in 6,413 PYLL compared with 45,958 PYLL for lung cancer (Australian Institute of Health and Welfare (AIHW) 2009d), 23,380 PYLL for colorectal cancer (Australian Institute of Health and Welfare (AIHW) 2009c) and 27,230 PYLL for breast cancer (Australian Institute of Health and Welfare (AIHW) 2009b). However, it should be noted that this measure may be flawed given that the PYLL beyond 75 years of age are not accounted for in this database, yet the average additional life expectancy of a man at the age of 50 years is 31.4 years compared with 14.7 years for a man at the age of 70 years (Australian Bureau of Statistics 2008). This will result in a relative underestimation of the PYLL among prostate cancer patients, who have a propensity to live to an older age than other cancer patients.

Potential utilisation

LDR ^{125}I BT for the treatment of localised prostate cancer is currently listed on the MBS for men with PSA < 10 ng/mL, Gleason score ≤ 7 and a clinical stage of T1 or T2. Predicting the potential utilisation of LDR ^{125}I BT is difficult given the lack of published national epidemiological data stratifying Australian prostate cancer patients by stage or grade. Recently, data from the South Australian (SA) cancer registry spanning 1998–2006 was found to be broadly comparable with an SA-based prostate cancer outcomes database that captured approximately 20% of prostate cancer diagnoses state-wide (Beckmann et al 2009). From a cohort of 2,329 patients, about 34% were found to be at low or intermediate risk and younger than 70 years of age at diagnosis. If this finding were generalisable to the Australian population, more than 5,000 men diagnosed in 2006 would potentially be eligible for LDRBT. However, not all intermediate risk patients from Beckmann et al (2009) are currently eligible for LDRBT, as some have PSA levels > 10 ng/mL.

In a large New South Wales (NSW)-based cohort study of 1,642 men younger than 70 years of age and diagnosed with localised (T1 or T2) prostate cancer during October 2000–02 (Smith et al 2010), nearly 90% were found to have a Gleason score of 7 or less, and nearly 70% were found to have a PSA of < 10 ng/mL. If the patients who refused consent (n=627) and the patients of those doctors who refused to participate (n=537) had a similar distribution of Gleason score and PSA, at least 1,800–2,000 men would have

been diagnosed with localised, Gleason score ≤ 7, PSA ≤ 10 ng/mL prostate cancer between 2000 and 2002. Data collection occurred over 2 years; thus, approximately 1,000 men from NSW may have been eligible for LDRBT in 2001 or 2002. Given that the incidence of prostate cancer has increased nearly 50% to 2006, 1,500 men from NSW may have been eligible in 2006 for LDRBT. The average annual incidence of prostate cancer in NSW between 2001 and 2005 represented about one-third of all incident prostate cancer cases in Australia. Therefore, based on 2006 rates, approximately 4,500 men Australia-wide may have been eligible for LDRBT. This calculation is in agreement with the estimation from the Beckman et al (2009) study above, and therefore an estimate of 5,000 men per year has been used for costing in subsequent sections of this assessment.

As rates of opportunistic PSA testing rise, numbers of patients eligible for LDR ^{125}I BT are also likely to rise, given that PSA levels at diagnosis will fall and more patients will be diagnosed with prostate cancer at a younger age. This is strongly supported by Australian Institute of Health and Welfare (AIHW) data, which show that the risk of being diagnosed with prostate cancer for men aged 80–84 years has not changed since 1982, whereas the risk of being diagnosed at younger than 65 years has increased from 1 in 111 in 1982 to 1 in 18 in 2006. While prostate cancer incidence has risen over the past 3 decades, the majority of this growth of incidence has occurred in younger men.

There are additional preconditions for LDR ^{125}I BT that incorporate gland volume and urinary function; however, these are not likely to exclude substantial proportions of men from treatment with LDRBT, particularly if the age at diagnosis continues to decrease. The proportion of men who will actually receive LDRBT is limited by factors other than eligibility. Over recent years the observed number of LDRBT procedures has likely been limited by access to these services, patient choice for competing treatment options and cost implications.

Table 3 Item numbers and utilisation for prostate brachytherapy and open prostatectomy

Procedural Code	Source		2001–02	2002–03	2003–04	2004–05	2005–06	2006–07	2007–08
MBS number – 15338: PROSTATE, radioactive seed implantation of	AIHW	Count	-	-	-	536	663	734	968
		Same day (%)	-	-	-	9.3	11.6	14.2	16.4
	Medicare	Count	46	136	224	305	376	390	687
1167: Open Prostatectomy	AIHW	Count	3,003	3,413	4,357	5,347	5,521	6,569	7,041

Sources: AIHW (2010) and Medicare Australia (2010)

In the 2007–08 financial year there were 968 recorded procedures associated with MBS item number 15338, which is specific to permanent ^{125}I BT for prostate cancer. Table 3 shows the steady increase in LDRBT procedures for prostate cancer since 2001 following the initial MSAC recommendation for interim funding. The AIHW data are sourced from the National Hospital Morbidity Database and are an accurate representation of the number of LDRBT procedures from 2004 onward. Before 2004 the database does not separate out other interstitial LDRBT procedures from prostate-specific procedures, and thus the data are unreliable. The Medicare data represent only those procedures that have attracted a Medicare reimbursement and therefore do not capture procedures for public patients in public institutions. Also, in Table 3 the AIHW data show an increasing proportion of patients that are flagged as having received 'same day' procedures.

Over the same period there has been a similar increase in RPs. Table 3 shows the number of open prostatectomies (ICD-10AM code 1167) performed. This may underestimate the true number due to the recent increase in robot-assisted laparoscopic prostatectomies in Australia. Not all patients who are candidates for prostatectomies are eligible for LDRBT; however, it is likely, if trends observed in the US (Cooperberg et al 2004) are mirrored in Australia, that LDRBT will increasingly replace RP as a treatment choice for patients with low-risk prostate cancer.

Existing procedures

The management of localised prostate cancer remains controversial. To date, there have been few studies that compare present-day treatments; consequently, most established treatments are considered to be equally effective. Early diagnosis resulting in many years' lead time and the long natural history of prostate cancer can make true measures of treatment outcomes difficult to ascertain in the short term. New treatments for prostate cancer may take more than a decade to adequately assess in terms of cancer control. In Australia the most commonly used options for managing localised prostate cancer are radical prostatectomy (RP), external beam radiotherapy (EBRT), brachytherapy (BT) and deferred treatment (active surveillance (AS)).

Comparators

Radical prostatectomy

RP is the surgical removal of the prostate gland and reconnection of the urethra to the bladder neck. It can be performed as an open procedure, either using a retropubic or perineal approach, or laparoscopically. The more common of the two open techniques is the retropubic, requiring an abdominal incision that allows concomitant removal of pelvic lymph nodes (lymphadenectomy). Retropubic prostatectomy became the standard approach in the 1980s after Patrick Walsh performed the first nerve-sparing prostatectomy (Eggleston & Walsh 1985). Radical perineal prostatectomy, which involves a small incision between the ischial tuberosities, tends to be a shorter operation with less blood loss, although identification and sparing of the neurovascular bundles is technically more difficult. If lymphadenectomy is required, a separate abdominal incision for open or laparoscopic removal can be used.

Laparoscopic prostatectomy and, more recently, robotic-assisted laparoscopic prostatectomy require several small incisions in the abdomen, into which a camera and surgical instruments are passed. The robotic-assisted laparoscopic approach involves a surgeon operating from a remote console by manipulating miniature robotic 'arms' and viewing the procedure rendered in three dimensions by dual fibre optic cameras. Both laparoscopic and robotic-assisted procedures tend to be minimally invasive and may result in reduced blood loss and reduced recovery time, and with comparable oncological outcomes, compared with the open approach (Rassweiler et al 2003).

RP is a major surgical procedure with an operating time of between 2 and 5 hours using either the open or laparoscopic technique. Due to the potential complications of the surgery and the anaesthetic required, it is primarily offered to younger men in their 60s who are otherwise healthy, and only rarely offered to men over the age of 75 years.

Deaths from RP are rare. Thirty-day surgical mortality has been estimated at 0.5%, although it increases with age and cardiovascular comorbidities (Alibhai 2005). Complication rates for RP are typically high and include transient urinary incontinence and erectile dysfunction. Side effects of RP are likely affected by volume of patients per surgeon, volume of patients per hospital, surgical training and learning curve (Urbanek 2009). Specialised high-volume centres have reported complication rates for long-term incontinence as low as 2% (Patel et al 2005) and a return to potency among men who were potent at baseline as high as 97%, with the assistance of phosphodiesterase 5 inhibitors (PDE-5) if required (Menon et al 2005).

The introduction of specialist centres and new techniques such as nerve sparing and robot-assisted laparoscopic surgery may reduce the generalisability of outcomes from historical series.

External beam radiotherapy

EBRT, or teletherapy, is the irradiation of the prostate gland from external sources. It is relatively non-invasive, although it may involve the placement of internal 'gold seeds' or fiducial markers to assist in the accurate localisation of the prostate before and during treatment.

Over the past 2 decades more accurate and higher dosing techniques have been developed, such as three-dimensional conformal radiotherapy (3D-CRT) and, more recently, intensity modulated radiotherapy (IMRT).

EBRT requires a pre-treatment CT scan, which is then loaded onto a specialised computer that allows a technologist to plan the treatment. Due to the difficulty of accurately localising the soft tissue of the prostate on CT, MRI scans are often fused with the CT image to allow more accurate delineation of the prostate. As the prostate is not a fixed organ, permanent fiducial markers may be inserted to allow it to be 'tracked' on a daily basis while receiving treatment. These improvements in the localisation of the prostate have enabled increases in overall dose to the target without increasing the dose to adjacent critical structures. Theoretically, this will improve cancer control without increasing complications associated with the irradiation of organs such as the bladder, rectum and bowel.

EBRT may result in urinary and rectal side effects and sexual dysfunction, even with newer techniques (Zelefsky et al 2006). Unlike surgery, which is more often associated with incontinence, urinary complications from EBRT tend to be irritative or obstructive in nature, and include urgency, pain and frequency. These symptoms tend to resolve within weeks following the completion of radiotherapy, and require only conservative management. Longer term complications are rare and include urethral stricture (Chrouser et al 2005), cystitis (Crew et al 2001) and radiation proctitis (Skwarchuk et al 2000).

Like RP, EBRT has changed substantially since its inception. Typical doses in Australia are currently around 74–78 Gy compared with doses during the two-dimensional planning era of 64 or 66 Gy. Oncological outcomes and side effect profiles have changed as well, making historical series difficult to generalise to current practice.

It is difficult to compare studies of EBRT with those of RP because patient groups often differ substantially. RP is rarely offered to men with locally advanced disease, although these patients may still be eligible for EBRT. The average age of men receiving EBRT for prostate cancer tends to be older; and men with multiple comorbidities, who may be

refused surgery, may still be eligible for EBRT (Desch et al 1996). Patients are likely to select a treatment based on its perceived efficacy and on the side effect profiles that each treatment offers. This may result in men who are particularly averse to particular side effects choosing treatment with lower likelihoods of those side effects. In the absence of randomised trials, it is consequently difficult to compare treatments with confidence that some of the side effect profiles have not been biased by the self-selection of patients for that particular treatment.

Active surveillance

AS involves forgoing immediate treatment and monitoring for signs of progression or advancing disease. Australian guidelines do not adequately describe the components or frequency of AS (Australian Cancer Network Working Party 2002) and the prevalence of its application in Australia is largely unknown. The increasing incidence of prostate cancer in countries that have introduced PSA testing has raised interest in AS as a management option in an attempt to reduce the number of men with indolent or very low risk prostate cancer being needlessly exposed to the side effects of radical treatment (Klotz 2005). The intent of AS is to initiate radical treatment once it is apparent that a cancer is no longer indolent. AS is distinguishable from 'watchful waiting' (Hardie et al 2005; Klotz 2005), a term more commonly used to describe the choice to forgo radical treatment altogether and introduce conservative treatment if the prostate cancer becomes advanced. It is therefore inappropriate to classify a man who would be too elderly or infirm, who is unlikely to benefit from radical intervention, as receiving AS if no treatment is offered. Despite this, the terms 'watchful waiting' and AS continue to be used interchangeably within the literature, although, for the purposes of this report, they are defined as above.

Due to the lack of standardised AS protocols and triggers for treatment, comparisons of outcomes from men on AS relative to other treatment options are difficult. A further complication lies in the lack of studies of men who select or are randomised to AS.

While the comparative effectiveness of AS remains unknown, a recent single-arm study has reported very promising results, with actuarial 10-year prostate cancer survival of 97.2% among low-risk men (Klotz et al 2010). Similar results from other case series have prompted international guidelines to encourage clinicians to offer AS to men with low-risk prostate cancer (National Comprehensive Cancer Network (NCCN) 2010; National Institute for Health and Clinical Excellence (NICE) 2008) and the initiation of randomised trials involving AS (Wilt 2008).

Marketing status of the technology

All therapeutic products marketed in Australia require listing on the Australian Register of Therapeutic Goods (ARTG). LDRBT requires multiple specific instruments including an applicator and seed-handling equipment, specialist software to allow pre-operative or intra-operative treatment planning, software that will allow the post-implant verification of implant adequacy, radiation physics devices to measure the activity of radioactive sources, and the radioactive seeds themselves. Several companies have BT sources (seeds) listed on the register.

Current reimbursement arrangements

LDRBT for prostate cancer was first included for reimbursement on the MBS in 2001 and continues to receive interim funding. There are five item numbers associated with the planning, localisation of the prostate and implantation of radioactive seeds by a urological surgeon in association with a radiation oncologist at an approved site (items 55603, 15513, 37220, 15338, 15539) (Australian Government Department of Health and Ageing 2010). Table 4 lists the MBS descriptors and reimbursement fees.

Table 4 Medicare Benefits Scheme item numbers and reimbursement for low-dose-rate brachytherapy for localised prostate cancer

MBS item	Descriptor	Fee	Benefit (75%)
37220	PROSTATE, radioactive seed implantation of, **urological component**, using transrectal ultrasound guidance, for localised prostatic malignancy at clinical stages T1 (clinically inapparent tumour not palpable or visible by imaging) or T2 (tumour confined within prostate), with a Gleason score of less than or equal to 7 and a prostate specific antigen (PSA) of less than or equal to 10ng/ml at the time of diagnosis. The procedure must be performed by a urologist at an approved site in association with a radiation oncologist, and be associated with a service to which item 55603 applies.	$986.90	$740.20
15338	PROSTATE, radioactive seed implantation of, **radiation oncology component**, using transrectal ultrasound guidance, for localised prostatic malignancy at clinical stages T1 (clinically inapparent tumour not palpable or visible by imaging) or T2 (tumour confined within prostate), with a Gleason score of less than or equal to 7 and a prostate specific antigen (PSA) of less than or equal to 10ng/ml at the time of diagnosis. The procedure must be performed at an approved site in association with a urologist.	$884.25	$663.20
15513	RADIATION SOURCE LOCALISATION using a simulator or x-ray machine or CT of a single area, where views in more than 1 plane are required, for brachytherapy treatment planning for ^{125}I seed implantation of localised prostate cancer, in association with item 15338	$289.75	$217.35
15539	BRACHYTHERAPY PLANNING, computerised radiation dosimetry for ^{125}I seed implantation of localised prostate cancer, in association with item 15338	$592.90	$444.70
55603	PROSTATE, bladder base and urethra, transrectal ultrasound scan of.	$109.10	$81.85

Source: Australian Government Department of Health and Ageing (2010) – http://www9.health.gov.au//mbs/search.cfm?pdf=yes – accessed 2 November 2010

Approach to assessment

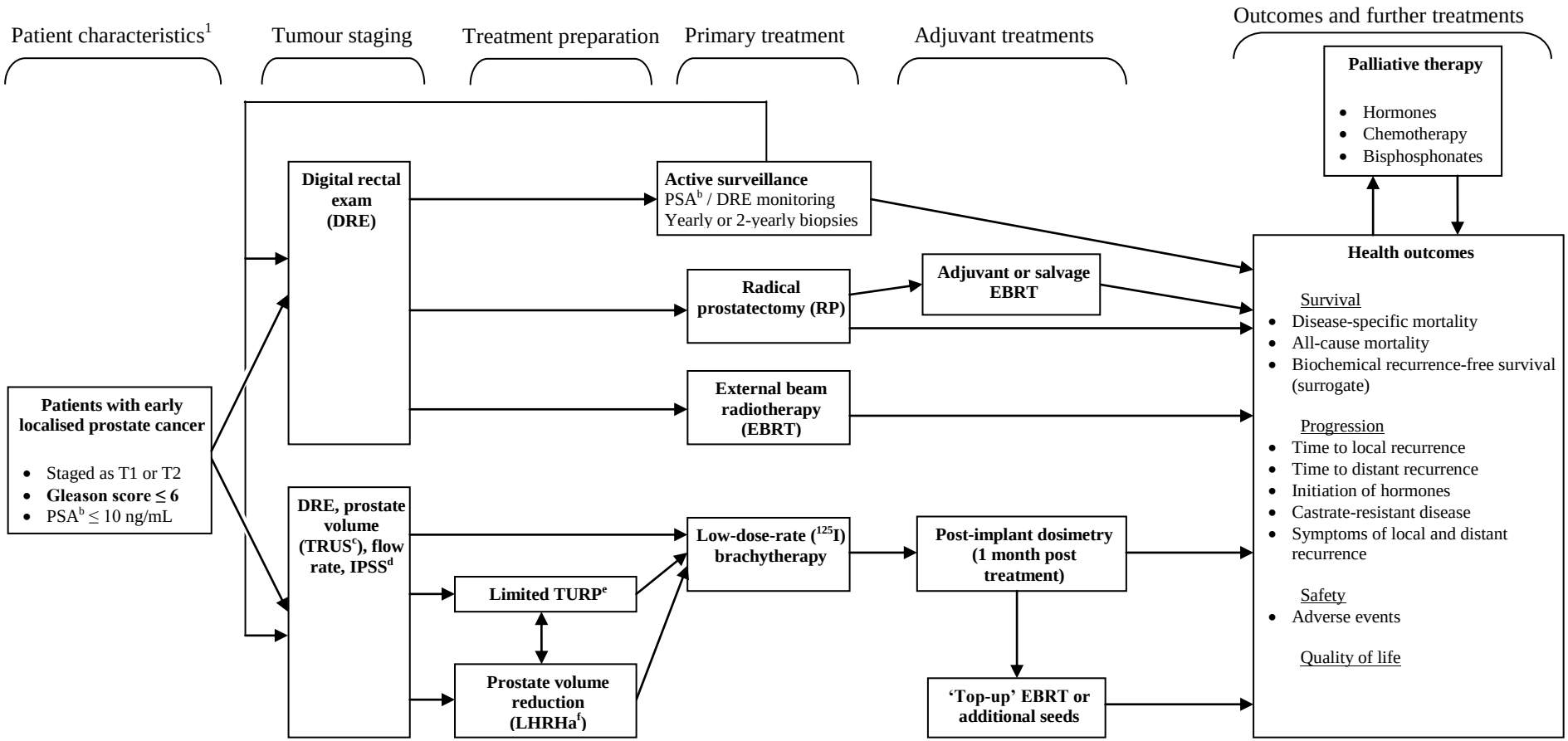
Objective

To determine whether there is sufficient evidence, in relation to safety, effectiveness and cost-effectiveness, to recommend public funding for low-dose-rate (LDR) iodine-125 brachytherapy (BT) performed as a monotherapy with curative intent for localised, low- to intermediate-risk prostate cancer.

Clinical pathway

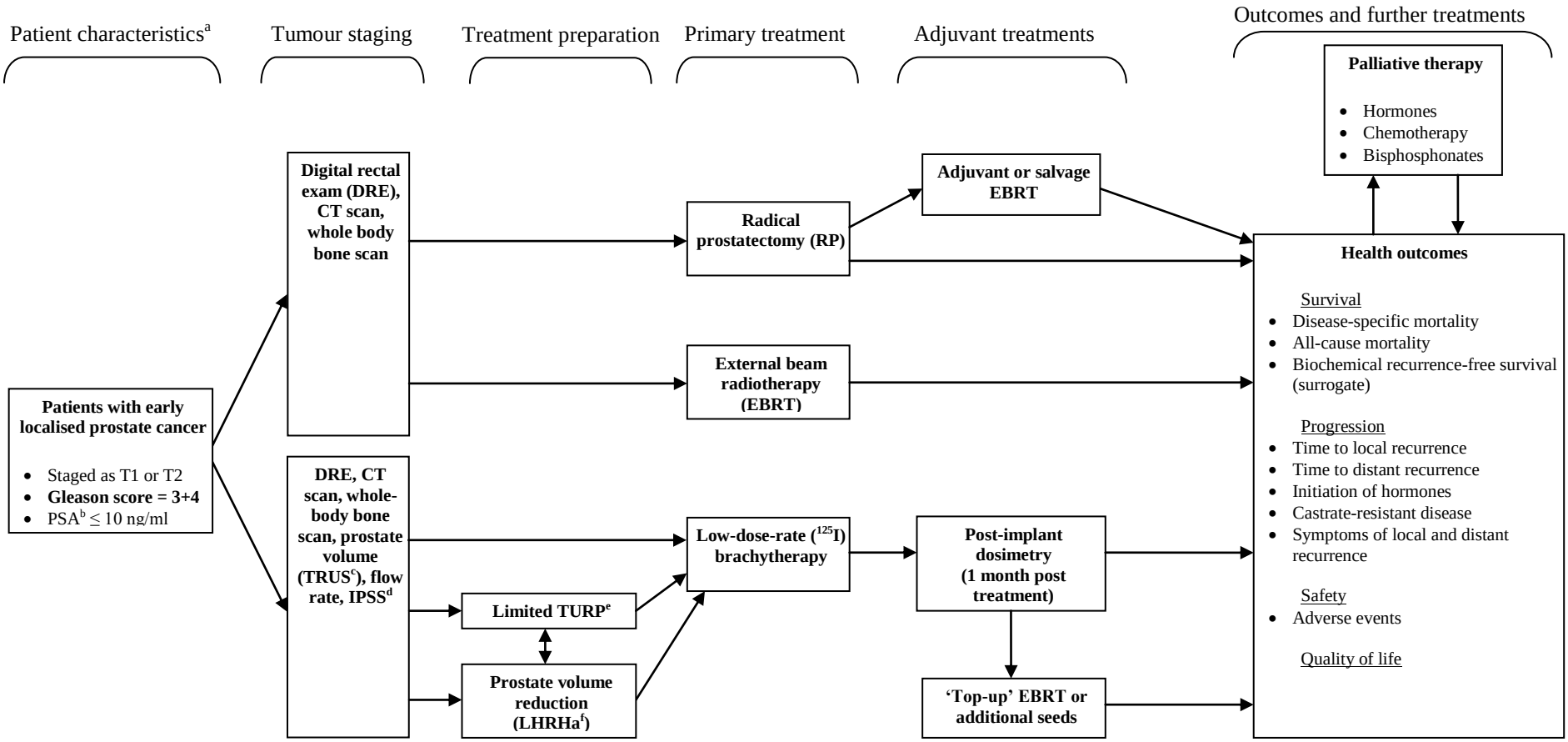
Flowcharts help to define the place of an intervention in the current clinical management of a disease. The placement of an intervention in a clinical pathway assists with the identification of the correct comparators, against which safety, effectiveness and cost-effectiveness can be measured. The suggested flowcharts provided in Figures 1–3 are clinical pathways developed in conjunction with, and agreed upon by, the Advisory Panel for this assessment of LDRBT for the treatment of prostate cancer. The flowcharts have been amended from those in the 2000 (Medical Services Advisory Committee 2000) and 2005 (Medical Services Advisory Committee 2005) LDRBT reviews to more precisely reflect the use of additional services and the inclusion of men with Gleason score 7 prostate cancer.

Figure 1 Clinical pathway for men diagnosed with localised prostate cancer with Gleason score = 6



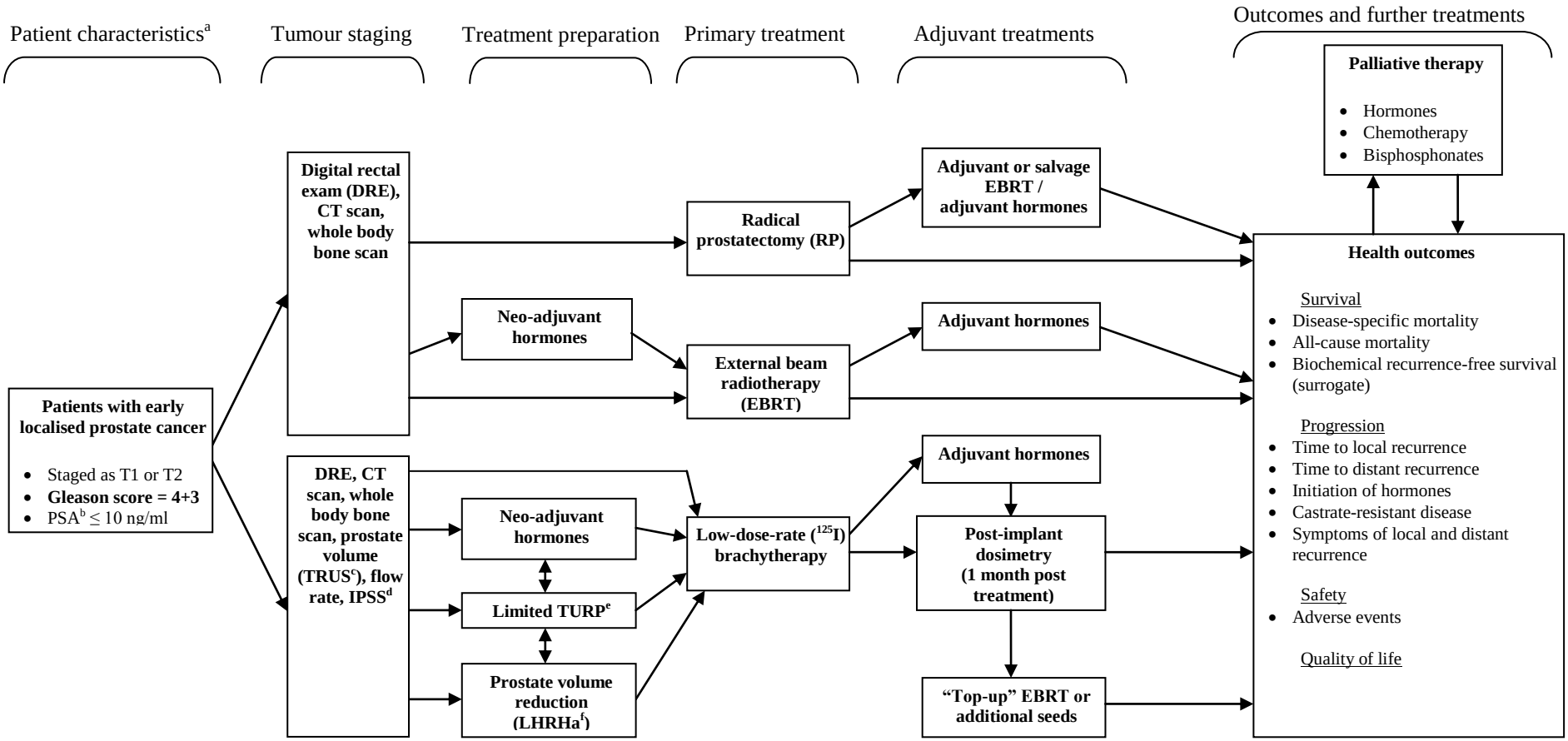
[a] See Table 2 for clinical staging and the section on Gleason score on page 7 for explanations; [b] PSA = prostate specific antigen; [c] TRUS = transrectal ultrasound; [d] IPSS = International Prostate Symptom Score; [e] TURP = transurethral resection of the prostate; [f] LHRHa = luteinising hormone-releasing hormone analogue

Figure 2 Clinical pathway for men diagnosed with localised prostate cancer with primary Gleason grade = 3 and secondary Gleason grade = 4 (Gleason score = 7)



[a] See Table 2 for clinical staging and the section on Gleason score on page 7 for explanations; [b] PSA = prostate specific antigen; [c] TRUS = transrectal ultrasound; [d] IPSS = International Prostate Symptom Score; [e] TURP = transurethral resection of the prostate; [f] LHRHa = luteinising hormone-releasing hormone analogue

Figure 3 Clinical pathway for men diagnosed with localised prostate cancer with primary Gleason grade = 4 and secondary Gleason grade = 3 (Gleason score = 7)



[a] See Table 2 for clinical staging and the section on Gleason score on page 7 for explanations; [b] PSA = prostate specific antigen; [c] TRUS = transrectal ultrasound; [d] IPSS = International Prostate Symptom Score; [e] TURP = transurethral resection of the prostate; [f] LHRHa = luteinising hormone-releasing hormone analogue

Comparator

The aim of this report is to evaluate the evidence of the safety, effectiveness and cost-effectiveness of LDR ^{125}I BT in the treatment of localised prostate cancer compared with radical prostatectomy (RP), external beam radiotherapy (EBRT) and active surveillance (AS).

Research questions

Safety

For patients with early localised prostate cancer.

1. What is the safety of low-dose-rate ^{125}I brachytherapy, compared with radical prostatectomy, external beam radiotherapy or active surveillance, in patients with localised prostate cancer?

Effectiveness

1. What is the effectiveness of low-dose-rate ^{125}I brachytherapy, compared with radical prostatectomy, external beam radiotherapy or active surveillance, in patients with localised prostate cancer whose total Gleason score is 6 or less?

2. What is the effectiveness of low-dose-rate ^{125}I brachytherapy, compared with radical prostatectomy, external beam radiotherapy or active surveillance, in patients with localised prostate cancer whose total Gleason score is 7 primarily made up of Gleason grade 3?

3. What is the effectiveness of low-dose-rate ^{125}I brachytherapy, compared with radical prostatectomy, external beam radiotherapy or active surveillance, in patients with localised prostate cancer whose total Gleason score is 7 primarily made up of Gleason grade 4?

Cost-effectiveness

1. What is the cost-effectiveness of low-dose-rate ^{125}I brachytherapy, compared with radical prostatectomy, external beam radiotherapy or active surveillance, in patients with localised prostate cancer whose total Gleason score is 6 or less?

2. What is the cost-effectiveness of low-dose-rate ^{125}I brachytherapy, compared with radical prostatectomy, external beam radiotherapy or active surveillance, in patients with localised prostate cancer whose total Gleason score is 7 primarily made up of Gleason grade 3?

3. What is the cost-effectiveness of low-dose-rate ^{125}I brachytherapy, compared with radical prostatectomy, external beam radiotherapy or active surveillance, in patients with localised prostate cancer whose total Gleason score is 7 primarily made up of Gleason grade 4?

Expert advice

An Advisory Panel with expertise in urology, radiation oncology, radiation physics and consumer interests was established to provide guidance to the Evaluators to ensure that the assessment is clinically relevant and takes into account consumer interests. In selecting members for advisory panels, the MSAC's practice is to approach the medical colleges, specialist societies and associations, and consumer bodies for nominees. Membership of the Advisory Panel associated with this application is provided in Appendix B.

Review of literature

Literature sources and search strategies

The medical literature was searched to identify relevant studies and reviews for the period between 2000 and May 2010. The previous MSAC review, performed in 2005, searched literature from 2000 to 2005; however, given the broadening of the eligibility criteria to include men with Gleason scores of 7, the Advisory Panel decided to readdress this period for additional literature regarding men with Gleason 7 prostate cancer. Table 5 describes the electronic databases that were used for this search. Table 6 describes the strategy used for searching Medline. Similar text words, indexing terms and use of Boolean operators were employed when searching the other databases. Other sources of evidence that were investigated are provided in Appendix C.

Table 5 Bibliographic databases

Electronic database	Period covered
CINAHL	2000 – 05/2010
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	2000 – 05/2010
Current Contents	2000 – 05/2010
Embase.com (including Embase and Medline)	2000 – 05/2010
Pre-Medline	2000 – 05/2010
Web of Science	2000 – 05/2010
EconLit	2000 – 05/2010

Table 6 Search strategy

Step	Search text
1	exp prostate/
2	exp prostatic diseases/
3	exp neoplasms/
4	exp carcinoma/
5	exp adenocarcinoma/
6	cancer$.mp.
7	tumour$.mp.
8	tumor$.mp.
9	malignan$.mp.
10	or/3-9
11	10 and prostat$.mp.
12	exp prostatic neoplasms/
13	1 or 2 or 11 or 12
14	exp brachytherapy/
15	brachy-therapy$.mp.
16	brachytherap$.mp.
17	(prostat$ adj3 implant$).mp.
18	(irradiation or radiation or radiotherap$).mp.
19	seed$.mp.
20	18 and implant$.mp.
21	((irradiation or radiation or radiotherap$) adj3 interstitial).mp.
22	("ldr" or low dose rate).mp.
23	((iodine or I) adj3 "125").mp.
24	(iodine adj3 implant$).mp.
25	or/14-17
26	or/19-24
27	25 or 26
28	13 and 27
29	Animals/
30	Humans/
31	29 not (29 and 30)
32	28 not 31
33	limit 32 to yr=2000-2010

Inclusion / exclusion criteria

In general, studies were excluded if they:

- did not address the research question;
- assessed high-dose-rate brachytherapy;
- assessed brachytherapy predominantly using an isotope other than ^{125}I;
- assessed brachytherapy provided in combination with external beam radiotherapy; or
- assessed brachytherapy in a population that would be ineligible for MBS reimbursement in Australia;
- were in a language other than English and were of a lower level of evidence than available studies in English;
- did not have the appropriate study design; or

- did not address, or provided inadequate data on, one of the pre-specified outcomes.

If the same data were duplicated in multiple articles, results from only the most comprehensive article were included. If articles with duplicate data provided different analyses relevant to this review, it is made explicit in the reporting that results are based on overlapping populations.

The inclusion criteria relevant to each of the research questions posed in this assessment are provide in Box 1, Box 2 and Box 3 in the Results section of this report.

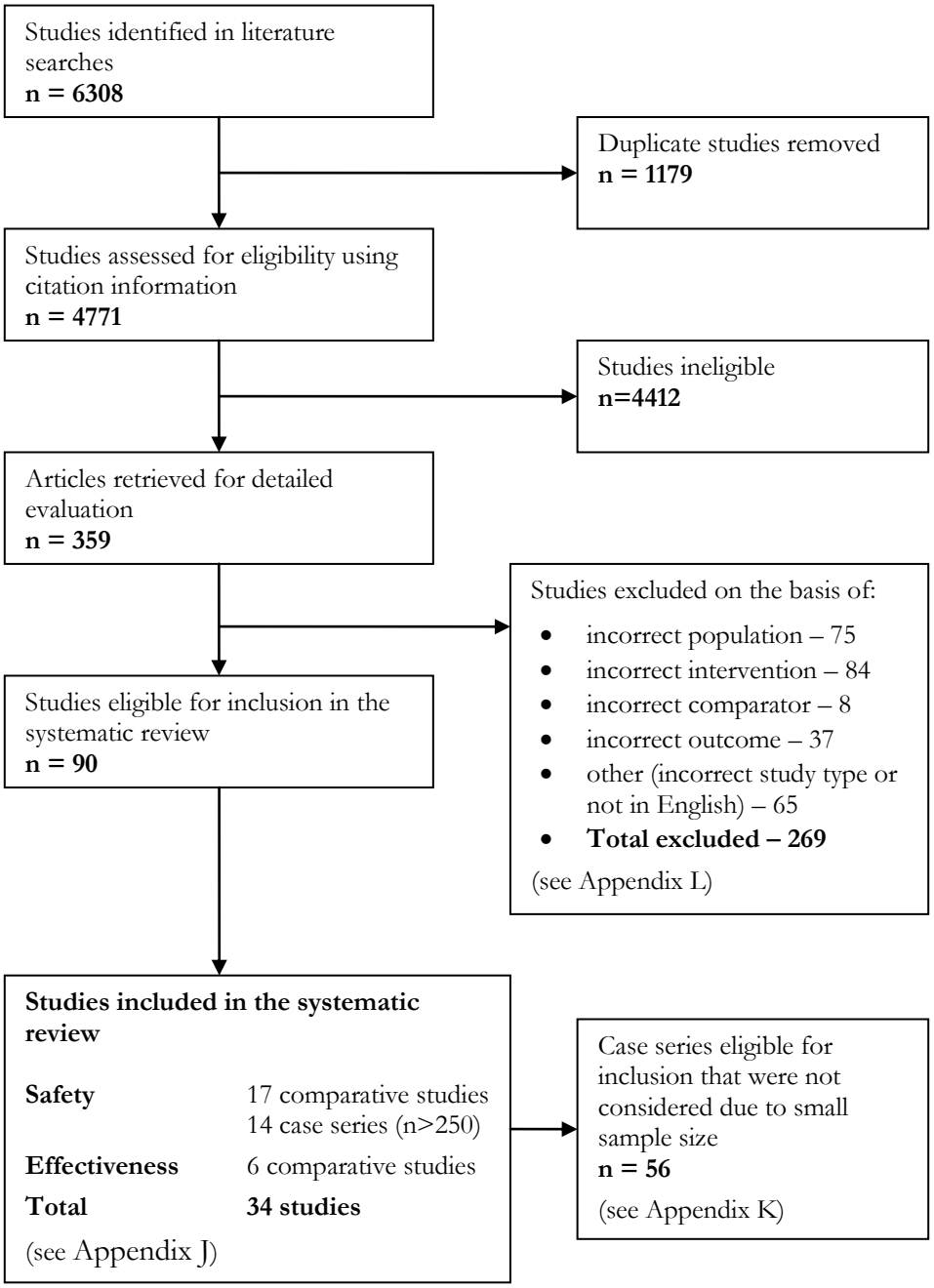
Search results

The process of study selection for this report went through six phases:

1. All reference citations from all literature sources were collated into an Endnote ™ X3 database.
2. Duplicate references were removed.
3. Studies were excluded, on the basis of the citation information, if it was obvious that they did not meet the pre-specified inclusion criteria. All other studies were retrieved for full-text assessment.
4. Studies were included to address the research questions if they met the pre-specified criteria applied by the reviewer on the full-text articles. Those articles meeting the criteria formed part of the evidence-base.
5. The reference lists of the included articles were pearled for additional relevant studies. These were retrieved and assessed according to phase 4.
6. The evidence-base consisted of articles from phases 4 and 5 that met the inclusion criteria.

   Any doubt concerning inclusion at phase 4 was resolved by consensus between two reviewers. The results of the process of study selection are provided in the PRISMA flowchart at Figure 4.

Figure 4 PRISMA flowchart outlining the process of study selection



Source: Liberati et al (2009)

Data extraction and analysis

A profile of key characteristics was developed for each included study (Appendix J). These study profiles describe authors, publication year, location of study, level of evidence, quality assessment, study design, study population characteristics, type of intervention, inclusion/exclusion criteria, outcomes assessed and follow-up period.

Comparative studies were available for the safety research questions. Time constraints limited the extraction of data from case series, and only case series with patient numbers greater than 250 were extracted. Case series that were found to be eligible but not extracted are listed in Appendix K.

Studies that were retrieved for full-text review but were found to be ineligible according to the inclusion criteria are provided in Appendix L.

Appraisal of the evidence

Appraisal of the evidence was conducted in three stages:

Stage 1: Appraisal of the applicability and quality of individual studies included in the review (strength of the evidence).

Stage 2: Appraisal of the precision, size of effect and clinical importance of the results for primary outcomes in individual studies—used to determine the safety and effectiveness of the intervention.

Stage 3: Integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

Validity assessment of individual studies

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC 2000).

These dimensions (Table 7) consider important aspects of the evidence supporting a particular intervention and include three main domains—strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention; the last two each require expert clinical input as part of its determination.

Table 7 Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design.[a]
Quality	The methods used by investigators to minimise bias within a study design.
Statistical precision	The p-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

[a] See Table 8

Strength of the evidence

The three subdomains (level, quality and statistical precision) are collectively a measure of the strength of the evidence.

Level

The level of evidence reflects the effectiveness of a study design to answer a particular research question. Effectiveness is based on the probability that the design of the study has reduced or eliminated the impact of bias on the results. The NHMRC evidence hierarchy provides a ranking of various study designs ('levels of evidence') by the type of research question being addressed (Table 8).

Table 8 Designations of levels of evidence according to intervention research question

Level	Intervention[a]
I[b]	A systematic review of level II studies
II	A randomised controlled trial
III-1	A pseudorandomised controlled trial (ie alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial[c] ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single-arm studies[d] ▪ Interrupted time series without a parallel control group
IV	Case series with either post-test or pre-test/post-test outcomes

Sources: Merlin et al (2009); NHMRC (2009)

[a] Definitions of these study designs are provided in NHMRC (2000), pp. 7–8, and in the accompanying Glossary.

[b] A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence.

[c] This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (ie using A vs B and B vs C to determine A vs C, with statistical adjustment for B).

[d] Comparing single-arm studies (ie case series from two studies).

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms (and other outcomes) are rare and cannot feasibly be captured within randomised controlled trials, in which case lower levels of evidence may be the only type of evidence

that is practically achievable; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.
Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question, eg level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Quality

Study quality was assessed for comparative studies using a validated checklist (Downs & Black 1998) that is able to appraise both randomised and observational studies. An overall determination of good, moderate or poor quality was allocated to studies based on reaching a minimum total score from the checklist, as well as reaching a minimum score for the bias and confounding components of the checklist (Table 9). The final question of the checklist regarding statistical power was not scored but sample size was considered during study appraisal. Quality appraisal for economic evaluations was performed using a checklist created by Drummond & Jefferson (1996). Quality appraisal for case series was performed using a checklist developed by NHMRC (2000).

Table 9 Quality assessment of studies with Downs and Black

	Overall score	Bias and confounding
Maximum score	*26*	*13*
Good	≥ 20	≥ 10
Moderate	16–19	6–9
Poor	≤ 15	≤ 5

Statistical precision

Statistical precision was determined based on narrow confidence intervals and small p-values, giving an indication as to the probability that the reported effect was real and not attributable to chance (NHMRC 2000). Studies needed to be appropriately powered to ensure that a real difference between groups could be detected in the statistical analysis.

Size of effect

For intervention studies of LDRBT and comparators it was important to assess whether statistically significant differences were also clinically important. The minimum effect size required for clinical importance was not predetermined and was assessed for each study after accounting for the likely impact of bias and confounding.

Relevance of evidence

The outcomes being measured in this report were assessed as to whether they were appropriate and clinically relevant. Inadequately validated (predictive) surrogate measures of a clinically relevant outcome were avoided (NHMRC 2000). Due to the long natural history of prostate cancer, and the absence of short-term clinically relevant outcomes, the surrogate marker of disease progression was assessed as a secondary effectiveness outcome for this review.

Assessment of the body of evidence

Appraisal of the body of evidence was conducted along the lines suggested by the NHMRC in their guidance on clinical practice guideline development (NHMRC 2009). Five components are considered essential by the NHMRC when judging the body of evidence:

- the evidence base—which includes the number of studies sorted by their methodological quality and relevance to patients
- the consistency of the study results—whether the better quality studies had results of a similar magnitude and in the same direction, ie homogeneous or heterogeneous findings
- the potential clinical impact—appraisal of the precision, size and clinical importance or relevance of the primary outcomes used to determine the safety and effectiveness of the intervention
- the generalisability of the evidence to the target population
- the applicability of the evidence—integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

A matrix for assessing the body of evidence for each research question, according to the components above, was used for this assessment (Table 10). Once the results of the studies were synthesised, the overall conclusion as derived from the body of evidence was presented to answer each clinical question—see the Discussion section (page 82).

Table 10 Body of evidence assessment matrix

Component	A	B	C	D
	Excellent	**Good**	**Satisfactory**	**Poor**
Evidence-base[a]	Several level I or II studies with low risk of bias	One or two level II studies with low risk of bias or a systematic review / multiple level III studies with low risk of bias	Level III studies with low risk of bias, or level I or II studies with moderate risk of bias	Level IV studies, or level I to III studies with high risk of bias
Consistency[b]	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population(s) studied in body of evidence are the same as the target population	Population(s) studied in body of evidence are similar to the target population	Population(s) studied in body of evidence differ to target population, but it is clinically sensible to apply this evidence to target population[c]	Population(s) studied in body of evidence are different to target population, and it is hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

Source: NHMRC (2009)

[a] Level of evidence determined from the NHMRC evidence hierarchy (Table 8)

[b] If there is only one study, rank this component as 'not applicable'.

[c] For example, results in adults that are clinically sensible to apply to children OR psychosocial outcomes for one cancer that may be applicable to patients with another cancer

Results of assessment

Is it safe?

All treatments for prostate cancer incur some risks to normal urinary, bowel and sexual function. These side effects may be acute or chronic and may have a considerable impact on patient quality of life. Quality of life is frequently deemed an effectiveness outcome in health technology assessments; however, as the aim of treatment for localised prostate cancer is primarily to prolong the life of commonly asymptomatic men, detriments in health-related quality of life following prostate cancer treatment almost invariably present as a consequence of treatment side effects, and hence are considered a function of treatment safety.

Low-dose-rate brachytherapy (LDRBT) for the treatment of early prostate cancer was assessed for potential patient harms resulting from the procedure. Inclusion criteria were developed a priori; however, they have been adjusted to reflect the data available for review. Specifically, the inclusion criteria for studies separated patients into groups based on Gleason score. However, the literature reported mixed populations of patients with both Gleason score 6 (or less) and Gleason score 7, and results were not presented in such a manner that they could be distinguished as distinct subgroups. For this review, therefore, these groups have been combined. While Gleason score is likely to be a strong prognostic marker for oncological and survival outcomes, it is less likely to affect safety outcomes (Andren et al 2006; Burdick et al 2009; Stark et al 2009). It is possible that patients with more aggressive cancers are treated more aggressively, and may experience greater treatment-related adverse effects; however, studies did not segregate groups on Gleason score for safety outcomes. Box 1 outlines the inclusion criteria for assessment of the safety of using LDRBT.

All reported rates of side effects are crude unless otherwise indicated.

Box 1 Inclusion criteria for studies assessing the safety of low-dose-rate brachytherapy for the treatment of localised prostate cancer

Research question	
1. Is low-dose-rate brachytherapy (LDRBT) as safe as, or safer than, radical prostatectomy (RP)?	
2. Is low-dose-rate brachytherapy (LDRBT) as safe as, or safer than, external beam radiotherapy (EBRT?	
3. Is low-dose-rate brachytherapy (LDRBT) as safe as, or safer than, active surveillance (AS) (no initial treatment)?	
Characteristics	**Criteria**
Population	Patients with early localised prostate cancer, defined as clinical stage T1 or T2, Gleason score ≤ 7 and a PSA ≤ 10 ng/mL. At least 85% of patients have met these criteria to be included, or patient groups were stratified such that the eligible cohort component was available for analysis. Animal or in-vitro studies were not included.
Intervention	Studies involve LDRBT with iodine^{125} permanent implants. Studies involving palladium^{103} were excluded if more than 50% of the sample receives ^{103}Pd, and patient outcomes were not stratified by radioactive source. Patients who received combined LDRBT with EBRT were not included in the analysis, and studies were excluded if data could not be separated.
Comparators	RP, EBRT and AS.
Outcome	Primary – urinary and bowel toxicities (obstructive and irritative urinary symptoms, urinary incontinence, proctitis, rectal bleeding and rectal complications, urethral stricture), sexual dysfunction or impotence, pain, secondary malignancies and treatment-related events causing patient death. Secondary – infection, pain, extended hospital stays.
Study design	Randomised or non-randomised controlled trials, cohort studies, case-control studies, registers, case series or systematic reviews of these study designs. Non-systematic reviews, abstracts, editorials, case reports, studies of less than 20 patients and laboratory studies were excluded.
Search period	January 2000 – May 2010. Studies reviewed as part of the previous MSAC reviews were excluded unless new information could be extracted from the study due to the expanded eligibility criteria.
Language	Studies in languages other than English were only translated and included if they represented a higher level of evidence than was available in the English language evidence-base.

Primary safety outcomes

Urinary side effects

The prostate gland is located at the bladder neck and entirely encompasses the first part of the urethra leaving the bladder. Surgical removal of the prostate gland or irritation of the gland, urethra or bladder by radiation may have consequences relating to normal urinary function. Urinary side effects following removal of the prostate (radical prostatectomy, RP) tends to be in the form of incontinence or dribbling, whereas radiation (brachytherapy, BT, or external beam radiotherapy, EBRT) tends to result in irritative symptoms such as dysuria and frequency, and obstructive symptoms due to oedema or stricture. Urinary function following treatment may have a substantial impact on overall quality of life and patient satisfaction with treatment. There may be considerable costs to the patient and the health system in managing severe cases of urinary side effects.

A total of 14 comparative studies were identified that met the selection criteria for assessing the urinary-related safety of LDRBT as a treatment for early prostate cancer. These studies are presented in Table 31 and are listed in order of NHMRC level of evidence and then quality. One study (Borchers et al 2004) was assessed in the previous MSAC review and was excluded, leaving 13 comparative studies. One randomised controlled trial (level II evidence) of moderate quality of 200 patients was identified that

compared RP with LDRBT (Giberti et al 2009). One moderate-quality large retrospective cohort study (level III-2 evidence) of 1,362 men compared LDRBT, RP, EBRT and AS (Smith et al 2010). Two prospective and two retrospective cohort studies (level III-2 evidence) of moderate quality of 960, 872, 841 and 304 men compared LDRBT, RP and EBRT (Ferrer et al 2008; Frank et al 2007; Guedea et al 2009; Wei et al 2002). The population included in Ferrer et al (2008), a multicentre cohort study, entirely encompasses that included in Guedea et al (2009), a single centre study; however, the analysis by Guedea is performed differently and so both have been considered in this review. It is made explicit when both studies are being considered. One matched comparison of two single-arm (level III-3 evidence), one prospective and two retrospective cohort studies (level III-2) of moderate quality of 278, 104, 374 and 809 men compared LDRBT and EBRT (Eade et al 2008; Pickles et al 2010; Pinkawa et al 2009; Wong et al 2009). Two prospective cohort studies (level III-2 evidence) of moderate quality of 213 and 435 men (Buron et al 2007; Hashine et al 2008) and one prospective cohort study (level III-2 evidence) of low quality of 94 men (Kirschner-Hermanns et al 2008) compared LDRBT and RP. Thirteen case series with study cohorts of greater than 250 men were also considered in this review. Of all included studies, only Smith et al (2010) (level III-2 evidence) was undertaken in Australia. Kirschner-Hermanns et al (2008) compared LDRBT with perineal RP, a surgical technique not commonly practised in Australia. The study profiles of all included studies are listed in Appendix J.

Measures of urinary side effects following treatment for prostate cancer are generally affected by two common symptom groups—urinary incontinence and lower urinary tract symptoms (LUTS), which are made up of irritative and obstructive symptoms. Side effects are reported as rates of incontinence, usage of incontinence pads, rates of men experiencing pain with urination, and frequency of urination; or by using scoring methods that combine several symptoms into an overall urinary function or urinary bother score. Comparison between studies that use different scoring tools can be problematic, as can the interpretation of an overall score given that multiple symptoms may affect its final sum. All reported rates are crude, unless otherwise specified.

Incontinence

Urinary incontinence (which may also be reported as the need to use pads) can occur following treatment for prostate cancer, in particular following RP. Incontinence was evaluated by seven studies of moderate quality and one study of poor quality. The timing of the assessment varies across the studies from immediately following treatment to 3 or more years following treatment.

Incontinence was higher following RP than LDRBT at 2 and 6 months (Buron et al 2007), 1 year (Buron et al. 2007), 2 years (Buron et al 2007; Ferrer et al 2008; Guedea et al 2009)[4] and 3 or more years (Frank et al 2007; Smith et al 2010) following treatment. In a randomised controlled trial (Giberti et al 2009), 18.4% of men receiving RP reported urinary incontinence at 6 months following treatment compared with none in the LDRBT arm.

Six studies compared LDRBT with EBRT in terms of urinary incontinence following treatment. Four studies did not show a difference between incontinence or pad usage

[4] The cohort reported by Ferrer et al (2008) entirely encompasses that studied by Guedea et al (2009).

between the groups (Guedea et al 2009; Ferrer et al 2008; Frank et al 2007; Wei et al 2002)[5], one study reported a greater usage of pads in men at 1 month following LDRBT compared with at the end of EBRT, but there was no difference at a time point approximately 16 months later (Pinkawa et al 2009); and one study reported low levels of incontinence at 3 years following treatment for both groups, although it did not report on effect sizes or statistical significance (Smith et al 2010).

The largest study to report on rates of incontinence is a population-based study by Smith et al (2010) with 1,362 patients eligible for this review. It is a moderate-quality report of level III-2 evidence and is the only study to involve an AS comparator. Urinary incontinence (as measured by the need to wear one or more pads per day) following RP at 3 years was reported as 12.3% compared with 5.4%, 2.7% and 3.4% for LDRBT, EBRT and AS respectively. This study was performed in Australia and has good external validity albeit with several limitations. Baseline characteristics of patients differed between the treatment groups, with 84.5%, 77.1%, 65.5% and 44.7% of men who received LDRBT, RP, AS and EBRT, respectively, reporting that they had private health insurance; and men who received LDRBT and RP having a comorbidity score of 2 or more approximately 25% of the time, compared with approximately 40% of men who received EBRT or AS. Another important source of bias arises from the time at which men responded to the baseline interview, in which they were asked to recall their symptoms at 1 month before treatment. The proportion of men who had already started treatment at the time of the initial interview varied from 88% who received RP to 36% who received LDRBT.

One comparative study from Germany reported results that conflicted with the other studies, with no difference in urinary incontinence between the LDRBT group and the RP group at 1 year. It did, however, report significantly lower pad usage ($p<0.001$) in the LDRBT group (Kirschner-Hermanns et al 2008). The authors reported incontinence in 52% of LDRBT patients at 1 year, a rate that is far higher than rates reported in any other study. The study was small, the surgical technique (perineal RP) is uncommonly used in Australia and the overall study quality is deemed to be poor. The same study did report that stress incontinence among men who underwent perineal RP remained significantly higher than the LDRBT group at 1 year (53% versus 18%, $p<0.001$), and the proportion of men experiencing stress incontinence was far lower than the proportion experiencing incontinence, raising questions of how 'incontinence' was defined by the authors. Due to inconsistencies in data and inadequate reporting, this result should be interpreted with caution.

Two case series involving more than 250 men reported quite different urinary incontinence rates following LDRBT. One case series (Matzkin et al 2003) of good quality reported no urinary incontinence following implantation. The second case series, of low quality (Schafer et al 2008), reported that 16% of men at a median of 51 months following treatment were using pads for incontinence. Neither study reported on baseline continence or pad usage.

One study modelled mean urinary incontinence subscales of the Expanded Prostate cancer Index Composite (EPIC) questionnaire, adjusting for age, use of hormones, risk group and baseline scores (Guedea et al 2009). The study reported, in comparison to

[5] The cohort reported by Ferrer et al (2008) entirely encompasses that studied by Guedea et al (2009).

LDRBT, that there was a statistically significant greater reduction (worsening) in mean urinary incontinence score at 2 years in men treated with RP. On the EPIC incontinence 100-point scale, relative to LDRBT patients, RP patients reported a mean decrease (worsening) in score of 11.45 points. While this is difficult to translate into rates of urinary incontinence, an 11-point difference on the questionnaire, adjusting for baseline scores, is very likely a clinically meaningful difference (Cella et al 2002; Osoba et al 2005). There was no difference between mean change from baseline for EBRT and LDRBT at 2 years after treatment.

Up to 1 year after treatment, reported rates of incontinence or pad usage varied from 68.4% to 13% following RP, 4% following EBRT, and nil to 17% following LDRBT. At follow-up longer than 1 year after treatment, reported rates were 12.3% to 49% for RP, 2.7% to 4% for EBRT, nil to 19.7% for LDRBT and 3.4% for AS.

Lower urinary tract symptoms

Irritative and obstructive symptoms were presented as a mean patient score using the EPIC questionnaire; International Prostate Symptom Score (IPSS); or as a proportion of men reporting urgency, LUTS, nocturia or pain with urination. In all comparative studies that reported on irritative or obstructive symptoms, LDRBT resulted in increased symptoms compared with RP at least up to 1 year in one study (Giberti et al 2009), with four studies reporting a continued difference beyond 1 year (Frank et al 2007; Ferrer et al 2008; Buron et al 2007; Wei et al 2002). Two of these studies reported differences in mean EPIC questionnaire score between the groups that are likely of little clinical significance.

Comparing EBRT with LDRBT, irritative or obstructive symptoms were worse following LDRBT in three studies at 16 months (Pinkawa et al 2009), 2.5 years (Wei et al 2002) and greater than 3.5 years (Frank et al 2007) following treatment, and no different in two studies measuring symptoms at 2 years following treatment. One study reporting a difference (Frank et al 2007) collected data at very different times following LDRBT and EBRT (median 3.5 years vs 4.7 years); if symptoms continued to improve with time several years after treatment, the results may be biased by the greater time for recovery in the EBRT arm. None of the studies that reported a difference between LDRBT and EBRT adjusted for baseline urinary function.

In the only randomised controlled trial (Giberti et al 2009), irritative and obstructive symptoms were presented using the IPSS (which is identical to the American Urological Association Symptom Score, AUASI). The score, ranging from 0 to 35 and with higher scores describing worse function, contains seven questions requiring a response along a 6-point Likert scale. All the symptoms described by the questionnaire—incomplete emptying, urinary frequency, intermittency, urgency, weak stream, straining and nocturia—are irritative or obstructive in origin. The trial found significantly increased symptoms at both 6 months and 1 year following LDRBT compared with baseline, but found no such increase in the RP arm. At 5 years there was no significant difference between IPSS and baseline in either treatment arm.

Guedea et al (2009) adjusted results for age, use of hormones, risk group and baseline EPIC irritative symptoms score, and reported that men receiving LDRBT worsened, on average, 4.76 points more than patients who received RP. While this is statistically significant, its clinical relevance is uncertain. It has been suggested that a clinically meaningful difference in quality of life scores is 5–10% of the scale breadth (Cella et al 2002; Osoba et al 2005); therefore, 4.76 points falls just below what might be considered

clinically meaningful on a 0–100-point scale. One major limitation of this study is the use of mean scores rather than proportions of patients who achieved a clinically meaningful change from their baseline score. It is therefore largely unknown whether a small number of patients experienced large changes or a large number of patients experienced small changes in their irritative or incontinence scores.

One consistent limitation of all but one of the included studies is the lack of a randomised design. Only two of the studies (Pinkawa et al 2009; Pickles et al 2010) attempted to match the baseline characteristics of LDRBT patients with the comparator group (EBRT). Both primarily matched upon known prognostic factors for treatment effectiveness, and one matched upon the incidence of comorbidities (Pinkawa et al 2009). Guedea et al (2009) used post-hoc statistical methods to control for multiple patient characteristics, including baseline urinary symptoms. No study, however, attempted to match patients on baseline urinary function, and this has been shown to be a strong predictor of function following treatment (Chen et al 2009). This, above all other sources of bias, introduces substantial uncertainty when interpreting these results. As it is a commonly held belief that treatments using radiation incur higher rates of obstructive symptoms, and surgery results in higher rates of incontinence, men already harbouring these symptoms before treatment may be less likely to be offered and more likely to decline these treatments. The most reliable results must therefore be drawn from the randomised controlled trial in which this bias cannot have occurred.

Urinary retention and urethral stricture

Urinary retention, or catheterisation rate, was reported by two studies of moderate quality. Giberti et al (2009), a randomised controlled trial, reported urinary retention following LDRBT in 10% of patients, and did not report retention among RP patients. A matched analysis of a LDRBT and EBRT cohort (Pickles et al 2010) reported that 15% of men who received LDRBT required catheterisation compared with none in the EBRT arm. Of the men who were catheterised, 42% remained catheterised for more than 1 month. This analysis matched patients on known risk factors for prostate cancer aggressiveness; however, it is not reported whether LDRBT and EBRT patients differed in pre-treatment urinary function, which would likely affect the urinary outcomes following treatment. The generalisability of this result to the present day is uncertain if the low median EBRT dose (68 Gy) of the study is associated with a reduced likelihood of urinary retention. However, this is deemed unlikely due to the characteristic timing of urinary retention in men receiving EBRT. Prostatic oedema tends to occur early in the course of radiotherapy for prostate cancer and may abate by the end of treatment or soon after, suggesting that it is unrelated to cumulative dose (expert opinion). It is probable that men who receive LDRBT are more prone to acute urinary retention than men treated with either RP or EBRT; however, the extent of that effect cannot be ascertained from these studies.

Seven case series with sample sizes greater than 250 men reported on rates of urinary retention. These rates were typically around 10% following LDRBT, ranging from as low as 2% to as high as 15%. The difference in reported rates is probably due to the differential use of corticosteroids intra-operatively and/or alpha blockers following seed implantation in each of the studies, as well as how closely bladder emptying is monitored.

A urethral stricture may require surgical intervention, result in urinary obstruction and/or substantially impair quality of life. One randomised controlled trial of 200 patients (Giberti et al 2009) reported urethral stricture rates of 2% among LDRBT patients and

6.5% among RP patients. One cohort study of moderate quality of 374 patients (Eade et al 2008) reported a urethral stricture rate of 7% (11 strictures) at a median time of 2.3 years following treatment among men receiving LDRBT compared with nil in patients receiving EBRT. In this latter study, patient baseline characteristics differed slightly between the groups; however, given that EBRT patients tend to be older, with larger prostates and higher baseline urinary morbidity, any associated bias is likely to be small or negative in direction. In both studies the LDRBT procedure is similar to that used in Australia, using either pre-operative or intra-operative planning. In the randomised controlled trial a dose delivered to 90% of the planned radiotherapy target (D90) > 140 Gy was deemed a good-quality implant; however, eight patients (of 158) from the cohort study were reportedly dosed to 160 Gy, although this was prior to the implementation of TG43 recommendations.[6] The effective dose is the same as 145 Gy, which was used following the implementation of TG43. The EBRT procedure was intensity modulated radiotherapy (IMRT) with a prescription dose to the planning tumour volume (5–6 mm posterior and 8 mm elsewhere beyond the prostate and proximal seminal vesicles) of 74–78 Gy. IMRT is not practised universally in Australia; however, current practice with 3D-CRT is likely to prescribe similar doses. One cohort study of moderate quality (Wong et al 2009) reported rates of treatment for strictures following 3D-CRT, IMRT and LDRBT of 2%, 2% and 14% respectively. However, the authors do not state what proportion of men received palladium implants; therefore, if there is a difference in the risk of stricture formation between the isotopes, it will be uncertain to what extent this result can be translated to the Australian context.

These rates of urethral stricture formation among LDRBT patients as reported by the comparative studies differ markedly (2% vs 7% vs 14%). Three case series with sample sizes greater than 250 men reported on rates of urethral stricture following LDRBT. The rates were 1.7%, 1% and 0.15%, all three being far lower than the percentage reported by either Eade et al (2008) or Wong et al (2009).

Questionnaire-rated urinary function and bother, and clinician-rated side effects

Urinary function is recorded by some instruments as an overall score whose sum may vary according to multiple side effects. These scores provide a method of comparing urinary side effects between treatments that are likely to result in different types of side effects. However, they are unable to describe the mix of symptoms that, together, resulted in the overall score. For instance, if a cohort who receive RP regard their urinary function as equal to that of a cohort who receive LDRBT, we cannot conclude that each treatment has equal side effect outcomes, but rather that the questionnaire has rated the mix of outcomes as having the same impact on global urinary function. This measure may be difficult to interpret, and indeed difficult for clinicians to advise patients who may be averse to one particular side effect but perhaps not another. Similar tools that often accompany measures of urinary function are questionnaires of urinary bother. These tools represent the impact of detriments in urinary function on everyday living. One final method of representing urinary side effects is by clinician-rated scales, in which specific side effects are classified on a scale of severity. As with patient-reported questionnaires

[6] American Association of Physicists in Medicine (AAPM) Task Group 43 (TG43) recommended standardised methods for the calibration, measurements of source strength and dose calculation formalism in the calibration. Dose prescriptions of 160 Gy using the Memorial Sloan-Kettering Cancer Centre (MSKCC) or Northwest Tumor Institute (NWTI) calculation methods are equivalent to prescriptions of 144 Gy using TG43 calculation methods (Bice et al 1998).‘ ’

that sum together urinary side effects, these scales are unable to describe the precise side effect profile that led to the final grade.

Four studies of moderate quality have reported on questionnaire scales that are not able to be separated into irritative/obstructive or incontinence scales. Three of the studies reported on separate function and bother scales, one using the University of California, Los Angeles Prostate Cancer Index (UCLA-PCI) questionnaire (Hashine et al 2008), and two using the EPIC questionnaire that was developed from the UCLA-PCI and has similarities (Smith et al 2010; Frank et al 2007). The final study, which also uses the EPIC questionnaire, reported on a summary score of the two urinary subscales (function and bother) (Ferrer et al 2008). All results are transformed to a 100-point scale. Hashine et al (2008) reported better urinary function for LDRBT compared with RP at 3, 6, 9 and 12 months following treatment; however, LDRBT patients also had significantly better urinary function at baseline (94.1±13.9 vs 88.9±19.4, p=0.027). As baseline function strongly predicts function after treatment, this may be an important source of bias. Urinary bother, measured in the same study, was greater among RP patients than LDRBT patients at 1 month and 12 months following treatment, although not at 3, 6 or 9 months. The UCLA-PCI questionnaire used by Hashine was primarily developed for use following RP and has fewer questions regarding irritative or obstructive symptoms resulting from radiation treatments. It is possible that the reported functional difference between the two groups results from the systematic inability of the UCLA-PCI to capture functional detriments following LDRBT.

The EPIC questionnaire is an extended version of the UCLA-PCI that was created to capture side effects from all prostate cancer treatments, but does not suffer the same measurement bias (Wei et al 2000). Frank et al (2007) used the EPIC questionnaire and, as stated previously, reported worse urinary incontinence among RP than EBRT and LDRBT patients, and worse irritative symptoms among LDRBT patients than both RP and EBRT. However, the study of 960 men was unable to show a difference in either overall urinary function or urinary bother at an average of 3.5, 4 and 4.7 years following LDRBT, RP and EBRT respectively. The final study (Smith et al 2010) reported that mean urinary function at 3 years was better for patients who received EBRT and LDRBT than patients who received nerve-sparing or non-nerve-sparing RP. Adjusting for age, baseline function, demographics and comorbidity score, all treatments had lower odds of having better urinary function than age-matched non-prostate-cancer controls at 1 year; however, only RP (nerve-sparing or non-nerve-sparing) continued to have lower odds (ie poorer urinary function) up to 3 years following treatment. The adjusted odds of having less urinary bother than an age-matched non-prostate-cancer cohort was lower for RP and LDRBT but not statistically significantly lower for EBRT at 1 year. The odds of having less urinary bother remained less than 1 for RP to 3 years, at which time EBRT and LDRBT were also lower, although LDRBT was no longer statistically significantly different from controls.

Three studies presented urinary side effects according to the Radiation Therapy Oncology Group (RTOG) morbidity grading system. Pickles et al (2010) reported acute grade 3 urinary side effects in 2.9% of LDRBT patients compared with only 0.7% (crude rate) of EBRT patients. Late urinary side effects (grade(s) unspecified) were more common in the LDRBT group (p<0.001). Late side effects scores were available for only 59% of the EBRT group and 83% of the LDRBT group. Reasons for incomplete data were not reported, and it is possible that the greater loss to follow-up in the EBRT group may have biased the results, in particular if patients with side effects were less inclined to continue participation in the study. The generalisability of the study results is uncertain given that

only 25% of the EBRT group received more than 68 Gy, which would be deemed an inadequate dose in today's practice. Eade et al (2008) also reported higher rates of acute and late urinary side effects in LDRBT patients compared with EBRT patients. Of the men who received LDRBT, 26.6% and 19.2%, respectively, suffered acute and late urinary side effects of RTOG grade 2 or greater, compared with 6.9% and 3.5%, respectively, for men who received EBRT ($p<0.001$, $p<0.001$). In contrast to Pickles et al (2010), the EBRT procedure doses to a similar level as current-day practice. Wong et al (2009) reported a significantly greater number of late RTOG grade 3 side effects among men who received LDRBT (18%) compared with those who received either 3D-CRT (5%) or IMRT (5%). This analysis reported on the maximum grade at any time following treatment (> 3 months) and therefore the duration of the side effects remains unclear. Because the proportion of men who received palladium implants is unknown in this study, there remains some uncertainty regarding its applicability to the Australian context.

One case series of 562 patients (Zelefsky et al 2007b) reported rates of 17% and 3% of RTOG late grade 2 and late grade 3 urinary side effects, respectively, following LDRBT.

Bowel side effects

The posterior margin of the prostate gland abuts the rectum and irradiation of this area is at risk of dosing both the rectum and other bowel segments. Acute gastrointestinal inflammation from irradiation is common, usually presenting as an increase in bowel motion frequency throughout treatment and then settling some months following the end of treatment. Chronic gastrointestinal symptoms, possibly related to the development of fibrosis, may range from merely a mild change in bowel habit to less common serious side effects such as fistulation, perforation or bleeding requiring a transfusion. Some side effects, such as enduring faecal incontinence, are likely to have serious implications for patient quality of life and may require invasive, unpleasant and/or costly intervention. Bowel symptoms may also occur following surgery for prostate cancer, in particular if the surgery results in direct damage to the rectal tissue or innervation.

A total of 16 comparative studies were identified that met the selection criteria for assessing the bowel-related safety of LDRBT as a treatment for early prostate cancer. These studies are presented in Table 32 and are listed in order of NHMRC level of evidence and then quality. One study (Borchers et al 2004) was assessed in the previous MSAC review and was excluded, leaving 15 comparative studies. One randomised controlled trial (level II evidence) of moderate quality of 200 patients was identified that compared RP with LDRBT (Giberti et al 2009). One moderate-quality, large retrospective cohort study of 1,362 men (level III-2 evidence) compared LDRBT, RP, EBRT and AS (Smith et al 2010). Five cohort studies (level III-2 evidence) of moderate quality of 1,584, 960, 872, 841 and 304 men compared LDRBT, RP and EBRT (Ferrer et al 2008; Frank et al 2007; Guedea et al 2009; Litwin et al 2004; Wei et al 2002). The population included in the study by Guedea et al (2009) is entirely encompassed by that included in the Ferrer et al (2008) study; however, analyses of Guedea add to the interpretation of bowel symptoms and so both studies have been included. One matched comparison of two single study arms (level III-3 evidence) and three cohort studies (level III-2 evidence) of moderate quality of 278, 104, 374 and 809 men (Pickles et al 2010; Pinkawa et al 2009; Eade et al 2008; Wong et al 2009) and one poor-quality retrospective cohort (level III-2 evidence) of 202 men (Tsui et al 2005) compared LDRBT with EBRT. Two cohort studies (level III-2 evidence) of moderate quality of 435 and 213 men (Buron et al 2007; Hashine et al 2008) and one cohort study (level III-2 evidence) of low quality of 212 men (Wyler et al 2009) compared LDRBT with RP. Five case series (level IV evidence) of study cohorts greater than 250 men have also been considered in this review. The study profiles of all included studies are listed in Appendix J.

Frequency, incontinence, pain and bleeding

Side effects may arise from irritation or damage to the colon, rectum or other bowel segments, and for simplicity are referred to as bowel side effects or toxicities. Bowel side effects may be reported as rates of individual symptoms, such as incontinence or painful bowel motions, or by using scoring methods that combine several symptoms into an overall function or bother score. Comparison of studies using different scoring tools can be problematic, as can the interpretation of an overall score given that multiple symptoms may affect its final sum. All reported rates are crude unless otherwise specified.

Three studies reported rates of bowel problems following treatment for prostate cancer. Pinkawa et al (2009) reported an increase in men with a moderate or big problem due to increased frequency of bowel movements at the end of their treatment in patients who received EBRT and at 1 month following treatment in patients who received LDRBT. At

a median of 16 months following treatment, LDRBT patients had a statistically lower proportion of men (2%) reporting moderate or big problems due to bowel frequency compared with EBRT (12%) patients. Faecal incontinence 2 years following treatment was reported to be worse than baseline in 2% and 8.9% of men who received RP and LDRBT respectively (Buron et al 2007). The authors did not provide a definition of faecal incontinence and therefore it is unclear whether very minor or infrequent incidents were included. As a result, it is difficult to draw conclusions regarding this outcome.

According to Pinkawa et al (2009), there was no difference in the frequency of men who received EBRT or LDRBT who reported bloody stools either immediately after treatment or at a median of 16 months. Bloody stools were reported by 17% and 12% of EBRT and LDRBT men at a median of 16 months following treatment. It should be noted that 8% and 12% of men receiving EBRT and LDRBT, respectively, reported bloody stools before treatment. It therefore appears that the proportion of men experiencing bloody stools following EBRT increased by 9% whereas it did not change in the LDRBT group. Pinkawa did not adjust for baseline rates and it is difficult to conclude whether there may have been a detectable difference had he done so. Conversely, Buron et al (2007) found that 15.1% of men receiving LDRBT reported more rectal bleeding at 2 years compared with no increase in rectal bleeding in the RP group.

The proportion of men experiencing painful bowel movements increased following treatment among those who received EBRT and LDRBT (Pinkawa et al 2009). At 1 month following LDRBT, 27% of men experienced painful bowel movements, which was significantly lower than the 52% of men in the EBRT group ($p<0.01$). At a median of 16 months following treatment, the proportion of patients experiencing painful bowel movements remained significantly lower in the LDRBT group compared with the EBRT group ($p<0.05$). This study has some serious limitations. Patient questionnaires were completed immediately following EBRT but only at 1 month following LDRBT. Delaying the questionnaire for LDRBT patients has some merit, given that the radiation dose for LDRBT is delivered slowly. However, no biological justification for the timing has been given. Also, 19% of patients in the EBRT arm reported painful bowel movements before treatment compared with 12% of patients in the LDRBT arm. This difference is not reported as statistically significant. However, as follow-up responses have not been adjusted for baseline differences, there is likely to be some confounding introduced into the results.

The final study reporting on the proportion of men experiencing bowel problems was a large Australian cohort (Smith et al 2010). At 3 years following treatment, 6.3%, 3.5% and 0% of men treated with AS, RP and LDRBT, respectively, reported moderate to severe bowel problems compared with 14.3% of men treated with EBRT. However, baseline bowel problems were vastly disparate between the groups, with 10.6% of men who were treated with EBRT reporting moderate to severe bowel problems. Without adjustment for baseline symptoms, there remains substantial uncertainty with regard to this finding.

Questionnaire-rated bowel function and bother, and clinician-rated side effects

Bowel function and bother following treatment can either be reported by the patient or assessed by the clinician. Of the patient-reported tools, multiple symptoms of bowel function and their effect on quality of life are summed together into overall scores. These can be represented as a function score and a bother score, often transformed to a scale of 100, or a combined score that encompasses both function and bother. Tools included in this review are EPIC, UCLA-PCI and the European Organisation for Research and

Treatment of Cancer Quality of Life Questionnaire – prostate cancer module (EORTC QLQ-PR25). Clinician-rated side effects are an assessment of the functional side effects of prostate cancer treatment on the bowel. RTOG morbidity scales report acute and late bowel side effects based on predefined criteria.

Eight included studies have reported on bowel function, bother or a combined score from patient symptom questionnaires. All eight compared LDRBT with RP, and in six studies RP patients reported better function, less bother or both at some time point following treatment. Importantly, one of the studies that found no difference (Guedea et al 2009) had an overlapping population with another larger study that showed a difference (Ferrer et al 2008); however, the methodology regarding how results were compared differed between the studies. Five studies compared LDRBT with EBRT, with four of these reporting better bowel function or bother in men receiving LDRBT. The largest study, involving 1,276 men treated with RP, 209 men treated with LDRBT and 99 men treated with EBRT, reported a difference in both UCLA-PCI scales of bowel function and bowel bother between the groups (Litwin et al 2004). In multivariate analyses controlling for time since treatment, PSA, Gleason score, clinical stage and comorbidities, treatment remained a significant predictor of bowel function and bowel bother. Despite this, the increase in bowel function of 2.0 and 5.9 points for LDRBT and RP, respectively, when compared with EBRT is of questionable clinical relevance given that the scale is 1–100. However, LDRBT and RP patients both reported bowel bother scores that were 7.1 and 9.4 points higher, respectively, than EBRT, when controlled for the above-mentioned factors. One shortcoming of the analysis is that it included responses from all follow-up time periods, many of which have small differences between the groups, and is therefore relatively insensitive to large differences in scores shortly after treatment. Absolute bowel function scores were substantially different between RP, LDRBT and EBRT immediately after treatment (within the first 3 months), with UCLA-PCI function scores of 75, 68 and 60 ($p<0.001$). Bowel bother for RP patients was significantly better than for EBRT and LDRBT patients ($p<0.001$), and bother for LDRBT patients was significantly better than for EBRT patients ($p<0.05$).

In an Australian-based cohort study (Smith et al 2010), unadjusted mean EPIC bowel function scores at 3 years following treatment were no different between men treated with LDRBT, EBRT, RP or AS. In contrast, bowel bother scores were significantly lower (worse) among men receiving EBRT (79.8) than all other treatments (90.0–90.5 for RP, 91.1 for LDRBT and 88.1 for AS). These scores are not adjusted for pre-treatment function or bother, and are difficult to interpret in light of possible baseline differences. Moderate or severe bowel symptoms at 3 years following treatment were reported by 14.5% of men who received EBRT, compared with nil, 3.5% and 6.3% of men who received LDRBT, RP and AS. More men who received EBRT reported moderate or severe bowel symptoms at baseline than those who received other treatments; therefore, this statistic is also prone to confounding.

One cohort study reporting on the EPIC bowel summary score (a combination of function and bother elements) found no statistical difference between the score at baseline and at 2 years in patients treated with RP, EBRT or LDRBT, both unadjusted and adjusted for age, risk group, use of ADT and baseline scores (Guedea et al 2009). A larger study encompassing the cohort of Guedea et al (2009) by Ferrer et al (2008) considered absolute EPIC score at 2 years rather than the change from baseline. It reported that RP had significantly greater (better) EPIC bowel scores than EBRT ($p<0.001$) and LDRBT had significantly greater EPIC bowel scores than EBRT ($p<0.001$), although these were unadjusted for confounders, including baseline bowel

function scores. The study by Guedea is, therefore, more methodologically accurate. In contrast to Ferrer et al (2008) and Guedea et al (2009), Wei et al (2002) found that men who received LDRBT had significantly lower (worse) bowel scores 2.5 years following treatment than men who received either RP or EBRT ($p<0.0005$). Wei modelled data taking into account time from treatment, age and prostate cancer specific predictors of survival. Baseline EPIC bowel scores, however, were not reported and so confounding from different baseline levels of bowel function cannot be ruled out. In addition, an unknown proportion of LDRBT patients were treated with adjuvant EBRT; therefore, the outcomes due to LDRBT alone may be influenced by those outcomes of dual-therapy patients.

In no study was bowel function or bother worse following RP compared with LDRBT, and in only one study was bowel function or bother worse following LDRBT compared with EBRT. As with all studies using mean scores, it is impossible to know whether a change in score represents a small global change in quality of life or a very large change for only a few.

Four studies comparing EBRT with LDRBT reported on clinician-rated bowel side effects using the RTOG morbidity scoring scheme. Comparing acute bowel side effects, two studies of moderate quality reported no difference in the incidence of grade 2 or higher side effects following EBRT or LDRBT. In one study by Wong et al (2009), acute gastrointestinal side effects were more common among men receiving IMRT or 3D-CRT than LDRBT ($p<0.001$). According to Wong, only 8% of men who received LDRBT experienced acute grade 2 or greater gastrointestinal side effects, compared with 54% of men who received 3D-CRT and 46% of men who received IMRT.

In one study involving IMRT prescribed to 74–78 Gy (Eade et al 2008), cumulative late grade 2 (or higher) side effects were significantly higher in the LDRBT group than the EBRT group at 3 years (7.8% vs 2.4%, $p=0.03$). This included one patient with grade 3 proctitis in the LDRBT group. Multivariate analysis, adjusting for age, diabetes, previous TURP, prostate size and initial AUA score, determined that LDRBT patients were three times more likely to suffer late grade 2 or higher side effects than IMRT patients ($p=0.05$). In contrast, Pickles et al (2010) reported an increased prevalence of late grade 3 (or higher) side effects in EBRT patients at 2–5 years following treatment ($p=0.018$). One limitation of this study is the low radiation doses prescribed to patients in the EBRT arm compared with present day, with only 25% receiving doses in excess of 68 Gy. It is possible that the rates of bowel side effects would increase with current EBRT prescriptions. The two conflicting studies have measured rates of side effects differently, with Eade et al (2008) opting to use a cumulative actuarial method and Pickles et al (2010) reporting on annual prevalence rates following treatment. Using the actuarial method does not allow for adjustments to be made when a side effect abates, and might be seen as a potential limiting factor of the analysis. It is possible that more men experienced late side effects in one group yet the side effects were shorter lived than the comparator, and an actuarial analysis would still present the former group as having higher toxicity. While Pickles et al (2010) matched patients from the two groups on common effectiveness prognostic factors, both studies suffer from a non-randomised design, and it is difficult to consider either study as methodologically superior.

One study of moderate quality (Wong et al 2009) and one of low quality (Tsui et al 2005) found no difference in the incidence of late grade 2 or greater bowel side effects between EBRT and LDRBT patients. Wong et al (2009) reported more frequent late grade 1 side effects among patients receiving 3D-CRT or IMRT than among patients receiving

LDRBT; however, grade 1 side effects can be treated conservatively and may not impact on patient quality of life.

Two case series involving 712 and 562 men reported RTOG late grade 2 or higher side effects among LDRBT patients in 9.8% and 7.0% of cases respectively.

Sexual dysfunction

Arising from the pelvic plexus, the autonomic innervation to the corpora cavernosa of the penis is delivered by the left and right neurovascular bundles. These microscopic nerves and vessels, first described by Walsh (Walsh & Donker 1982), are close to the prostate and are partly responsible for achieving normal erectile function. Historically, surgical removal of the prostate involved a wide resection of the neurovascular bundles, and post-surgery erectile dysfunction was frequent. Developments in prostate surgery, first described by Walsh (Walsh et al 1983), have enabled the identification and preservation of the neurovascular bundles, with some improvements in erectile function following treatment. Erectile function may also be affected following treatments using radiation; and, although irradiation of nerves or erectile tissue has been postulated as the cause, the mechanisms of post-radiation erectile dysfunction remain unclear.

A total of 11 comparative studies were identified that met the inclusion criteria for assessing the sexually related safety of LDRBT as a treatment for early prostate cancer. These studies are presented in Table 33 and are listed in order of NHMRC level of evidence and then quality. One study (Borchers et al 2004) was assessed in the previous MSAC review and was excluded, leaving 10 comparative studies. One randomised controlled trial of moderate quality of 200 patients was identified that compared RP with LDRBT (Giberti et al 2009). One large cohort study of moderate quality of 1,362 patients compared RP, LDRBT, EBRT and AS (Smith et al 2010). Four cohort studies, all of moderate quality, of 960, 872, 841 and 304 men compared RP, LDRBT and EBRT (Ferrer et al 2008; Frank et al 2007; Guedea et al 2009; Wei et al 2002). As stated previously, Ferrer et al (2008) entirely encompassed the population within the Guedea et al (2009) single centre study; however, the latter presented a different analysis and so has been retained in this review. Two cohort studies of moderate quality of 435 and 213 men compared RP and LDRBT (Buron et al 2007; Hashine et al 2008). One study of matched single arms (level III-3 evidence) of moderate quality of 104 men (Pinkawa et al 2009), and one poor-quality retrospective cohort (level III-2 evidence) of 202 men (Tsui et al 2005), compared LDRBT and EBRT. Four case series with study populations greater than 250 men were also considered in this review. The study profiles of all included studies are listed in Appendix J.

Erections adequate for intercourse

Erectile function may be reported either as rates of potency among men or by examining sexual function as reported by patients on specific sexual function questionnaires. Potency rates are perhaps most easily measured and interpreted; however, they lack insight into quality of life aspects that will be captured by instruments measuring sexual bother. Four studies have reported rates of potency, erections adequate for intercourse or changes in erectile function from baseline. A study on a large Australian cohort of 1,362 men reported on impotence rates (defined as 'unable to obtain an erection sufficient for intercourse') in men treated with RP, EBRT, LDRBT and AS. It found that rates of impotence differed markedly before treatment, with the highest rates (30.2%) in EBRT patients and the lowest (15.6%) in nerve-sparing RP patients (Smith et al 2010). The baseline impotency rate among men opting for LDRBT was 19%, with 27.3% among those opting for AS and 27.6% of men opting for non-nerve-sparing RP. The mean age between the groups was also different, perhaps partly explaining the disparity in impotency rates; however, it is possible that the differences also represent patient selection of treatments more favourable for sexual function outcomes. At 3 years

following treatment, rates of impotency had increased across all treatments, to 86.7% among men receiving non-nerve sparing RP (the highest reported rate) and 36.4% of men receiving LDRBT (the lowest reported rate). Rates of impotence had substantially increased for men who opted for AS; however, 14% of men had been treated within the follow-up period (many with RP) and therefore the mean results would have been influenced by the side effects experienced by those treated. Importantly, impotency rates were lower following LDRBT than nerve-sparing RP (36.4% vs 67.9%), which cannot be biased by disparate baseline rates given that baseline impotency was lower among men opting for nerve-sparing RP. While a large number of men (primarily those with good baseline function) reported the use of phosphodiesterase-5 (PDE5) inhibitors, after adjusting for age, baseline potency and treatment type, the use of PDE5 inhibitors appeared to have no effect on potency at 3 years.

Two studies compared potency rates following treatment among men receiving LDRBT and EBRT. Including only men potent at baseline, Pinkawa et al (2009) found no difference between post-treatment potency rates following LDRBT (67%) and EBRT (51%). However, the numbers included in this sub-analysis (29 and 31 for LDRBT and EBRT respectively) are far too small to determine whether the observed difference of 16% between the samples was statistically significant; therefore, the lack of significance may be due to a type 2 error. Tsui et al (2005) reported that potency rates in men who were potent before treatment and who did not receive androgen deprivation therapy (ADT) as part of treatment were higher at 12 months following LDRBT (95.7%) than EBRT (68.8%). This analysis has some serious limitations. Firstly, ADT was used in almost one-third of LDRBT patients, and potency rates are entirely unknown for this group. This may bias the study if, in men for whom potency is a high priority, adjuvant ADT with LDRBT was less frequently used. In addition, the authors report that the use of PDE5 inhibitors was encouraged in men who received LDRBT, whereas it was seldom offered to men following EBRT.

One study compared potency rates among sexually active men receiving RP and LDRBT, and found that at 6 months following treatment, 88% and 50.8% of men, respectively, reported poorer erectile function than at baseline (Buron et al 2007). By 18 months following treatment, 83.3% and 45.8% of men treated with RP and LDRBT, respectively, continued to report erectile function diminished from baseline. The use of treatment for impotence was not equal between the groups; however, it was higher among the RP group than the LDRBT group (32% vs 12.5%) and therefore the results should be interpreted with caution.

Questionnaire-rated sexual function and bother

Erectile function may be reported using patient answered questionnaires, such as EPIC, UCLA-PCI, IIEF or EORTC QLQ-PR25. The EPIC and UCLA-PCI questionnaires are transformed into a scale of 0–100, with higher scores representing better outcomes. Both the EPIC and UCLA-PCI have a sexual outcome specific component that can be presented either as function and bother subscales or as a combined score. The IIEF score exists as a 15-item and an abridged 5-item (commonly termed the sexual health inventory for men) questionnaire. The EORTC QLQ-PR25 contains a sexual module of six questions, which is transformed to a scale of 0–100. Higher scores on all questionnaires require adequate erections for intercourse, and may be a surrogate for erectile function. However, a good score on any questionnaire also requires some level of sexual activity, which may be contingent upon variables unrelated to function, such as emotional and

mental status, motivation, other treatment-related sequelae and the existence and sexual function of a partner.

Seven studies reported on patient-answered questionnaires. One randomised controlled trial of 200 patients (Giberti et al 2009) reported a significant reduction in mean IIEF score at 6 months following both RP and LDRBT ($p=0.02$ and 0.03 respectively). At subsequent time points (1 and 5 years), mean IIEF in both groups was no different from baseline. The authors report a significantly greater proportion of men regaining erectile function (defined as an IIEF > 22) in the LDRBT group than the RP group at both 6 months (58% vs 40%) and 1 year (78% vs 68%) following treatment, although it is unclear whether these figures represent the entire study cohort or only men with good erectile function before treatment. There was no difference between treatment groups at 5 years following treatment. The quality of reporting by Giberti et al (2009) is poor and it is unclear whether the entire study population responded to this questionnaire or whether it was a subgroup analysis. The use of erectile aids is not reported, statistical comparisons report on change from baseline rather than differences between groups, and losses to follow-up are not considered in the analysis. This result should therefore be considered with caution.

A large Australian study of 1,362 men comparing RP, EBRT, LDRBT and AS (Smith et al 2010) found that mean UCLA-PCI sexual function scores for each group were lower 3 years following treatment compared to baseline. After adjusting for age, baseline sexual function, comorbidity score and demographic variables, men treated with EBRT, LDRBT or AS had higher odds of having better sexual function at 3 years following treatment than an age-matched group of men without prostate cancer, and compared with men treated with either nerve-sparing or non-nerve-sparing RP. Sexual bother also worsened across all treatments but was worse among patients receiving RP. This study represents 64% of all men diagnosed with localised prostate cancer in NSW who were aged less than 70 years at diagnosis. A strength of the study is that it represents outcomes of men who are treated at centres with varied levels of expertise and patient volume. However, eight urologists with higher than average patient volumes declined to participate in the study. It is likely that surgical volume and experience is a predictor of post-operative erectile function (Meuleman & Mulders 2003), and the reported rate of impotence among men treated with RP in Smith et al (2010) may therefore represent an overestimation.

Of the remaining five studies that reported on sexual questionnaires, four compared RP, EBRT and LDRBT, and one compared RP and LDRBT. Four of the five studies involving RP (Ferrer et al 2008; Frank et al 2007; Guedea et al 2009; Hashine et al 2008) showed better retention of potency following LDRBT than RP; however, the 304 patients studied by Guedea et al (2009) are also included in the Ferrer et al (2008) cohort of 841 patients. Adjusting for age, baseline scores, risk group and hormonal treatment, Guedea reported that LDRBT patients retain, on average, 18.74 more points on a 0–100 EPIC sexual summary scale at 2 years following treatment. While Hashine et al (2008) did not adjust for baseline score, the authors reported significantly better UCLA-PCI sexual function among men receiving LDRBT at 1, 3, 6 and 12 months following treatment *despite* LDRBT patients starting with a lower mean sexual function. Wei et al (2002), the only study not to show a difference, reported no difference in EPIC sexual score between LDRBT and RP patients at 2.5 years following treatment, but did not control for, or report, baseline sexual function. While this result is a prediction from a multivariate model adjusting for, among other things, use of hormone therapy, it is still worth noting that more than half of all LDRBT patients received adjuvant or neo-adjuvant hormone antagonists compared with 28% of RP patients ($p<0.01$). In addition, an unknown

proportion of LDRBT men were treated with adjuvant EBRT; therefore, it is uncertain how generalisable this result is to LDRBT delivered as monotherapy.

Sexual bother was reported to be worse following RP in one study (Hashine et al 2008), and no different in another (Frank et al 2007), compared with LDRBT. As bother tends to decline with time, this disparity may be due to differences in the timing of the assessment of sexual bother. Hashine reported a difference between LDRBT and RP at 12 months, which is far closer to the treatment than the assessment by Frank that occurred at an average of 3.5 years and 4 years post LDRBT and RP respectively.

In the four studies that compared LDRBT with EBRT, two studies reported that LDRBT patients had significantly better sexual function or overall sexual score than EBRT following treatment (Ferrer et al 2008; Frank et al 2007). Neither study reported on baseline functioning and therefore it is unknown whether erectile function may be influenced by treatment selection based on patient preference. In a study of 304 patients, all of whom are included in the study by Ferrer et al (2008), no difference in sexual functioning at 2 years following treatment could be detected between men who received EBRT and LDRBT once the scores were adjusted for age, baseline scores, risk group and use of ADT. In a cohort study involving 872 patients (Wei et al 2002), EPIC sexual score was significantly lower (worse) at 2.5 years following LDRBT than EBRT. Baseline sexual function was not reported and so it is unclear whether confounding has affected the results. Also, as an unknown number of LDRBT patients also received EBRT, the generalisability of this result to the Australian context is uncertain.

Two case series of 643 and 342 patients reported potency rates following LDRBT among men who were potent before the procedure. At 1, 2, 3 and 5 years following LDRBT, potency was reported in 30%, 34%, 86.8% and 73.4% of patients respectively.

General health-related quality of life

In addition to urinary, bowel and sexual function or bother, researchers are also interested in the impact of prostate cancer and its treatments on general quality of life. Quality of life following treatment for prostate cancer is likely to be, at least in the short term, a function of the side effects of the treatment, and impairments in quality of life can therefore be viewed legitimately as safety outcomes. Given the difference in the side effect profiles of prostate cancer treatments, general quality of life measures have the advantage of drawing together the overall impact of quite disparate side effects into one meaningful score. While this allows easier comparison of treatments, it lacks the descriptive benefits of more symptom-specific scores, which may be important to consumers who have greater aversion to some side effects than others.

A total of 11 comparative studies were identified that met the inclusion criteria for assessing post-treatment quality of life related to safety of LDRBT as a treatment for early prostate cancer. These studies are presented in Table 34 and are listed in order of NHMRC level of evidence and then quality. One study (Borchers et al 2004) was assessed in the previous MSAC review and was excluded, leaving 10 comparative studies. One randomised controlled trial (level II evidence) of moderate quality of 200 patients was identified that compared RP with LDRBT (Giberti et al 2009). One moderate-quality, large cohort study (level III-2 evidence) of 1,362 patients compared RP, LDRBT, EBRT and AS (Smith et al 2010). Four cohort studies (level III-2 evidence) of moderate quality of 90, 841, 304 and 872 men compared RP, LDRBT and EBRT (Ferrer et al 2008; Guedea et al 2009; Lee et al 2001; Wei et al 2002). The population studied by Guedea et al (2009) is entirely encompassed by that reported by Ferrer et al (2008). Two moderate-quality cohort studies (level III-2 evidence) of 435 and 213 men (Buron et al 2007; Hashine et al 2008), and two cohort studies of poor quality of 212 and 94 men (Kirschner-Hermanns et al 2008; Wyler et al 2009) compared RP and LDRBT. The study profiles of all included studies are listed in Appendix J.

One randomised controlled trial of moderate quality comparing general quality of life outcomes following RP and LDRBT reported a significant decrease in all components of the European Organisation for Research and Treatment of Cancer Quality of life Questionnaire (EORTC QLQ-C30) at 6 months for both treatments, with the exception of cognitive function, which was significantly reduced in RP patients only. By 1 year following treatment, only the physical function and emotional function components of the questionnaires remained significantly lower than baseline, and by 5 years all components of the EORTC QLQ-C30 were no different from before treatment. Giberti et al (2009) performed no comparative statistics, and differences in baseline scores make direct comparisons problematic.

For the nine remaining studies comparing RP and LDRBT, there were mixed results. In the study by Kirschner-Hermanns et al (2008), men treated with RP reported a higher emotional functioning component of the EORTC QLQ-C30 at 1 year. However, no data on baseline functioning were presented. Wei et al (2002) reported a significantly greater (better) Functional Assessment of Cancer Therapy – prostate module (FACT-P) score among men treated with RP than those who received LDRBT at 2.5 years; however, baseline scores were unavailable and confounding cannot be ruled out. Using EORTC QLQ-C30, Wyler et al (2009) reported no difference between men treated with LDRBT and RP, with the exception that LDRBT patients reported a higher score for the cognitive function component at 25–36 months following treatment. Given the lack of

differences in other quality of life components, and at other time points, this finding is difficult to interpret. It is possible, due to the very small numbers of questionnaires at this (and all other) time points, that this represents a type 1 error. Hashine et al (2008) and Ferrer et al (2008), both using the Short Form–36 (SF-36) health survey, reported significant differences in almost all the SF-36 components at 1 month, with LDRBT outperforming RP. By 3 months LDRBT scores were higher than RP scores in only role function and body pain (Ferrer et al 2008) and role emotional and role physical (Hashine et al 2008). Differences did not extend beyond 12 months in either study, and at no time point for any components in either study did RP patients report a higher mean score than LDRBT patients. Smith et al (2010) adjusted for age, baseline score, comorbidities and demographic variables, and reported results from the Short Form–12 (SF-12) health survey at 1 year. No treatment showed a difference in physical component score than age-matched non-prostate cancer controls, and only RP patients showed lower odds of having a higher mental component score than age-matched non-prostate cancer controls. No differences were reported beyond 1 year. Buron et al (2007), using the EORTC QLQ-C30, reported significantly smaller detriments in scores for LDRBT at the end of treatment compared with RP, although by 2 months the LDRBT group remained better only for the role function component of the QLQ-C30. At all later time points (from 6 months through to 2 years), RP patients reported an improvement in global quality of life score from baseline that was significantly greater than for those men treated with LDRBT.

Five studies compared general quality of life following treatment with LDRBT and EBRT. Ferrer et al (2008) reported higher SF-36 scores for bodily pain and physical function at 6 months for patients treated with LDRBT compared with those receiving EBRT. No differences in SF-36 extended beyond 6 months. Lee et al (2001) reported no difference in quality of life beyond 12 months comparing LDRBT and EBRT groups using the FACT-P questionnaire. However, the authors did report a significantly greater worsening in FACT-P among LDRBT patients compared with EBRT patients at 1 month. Wei et al (2002), who modelled FACT-P scores adjusting for age, time since treatment and pre-treatment cancer severity, found that LDRBT performed significantly worse than EBRT at 2.5 years. In this study pre-treatment health-related quality of life values were not available; hence, unmeasured baseline differences in FACT-P may contribute to the modelled differences at 2.5 years. Smith et al (2010) and Guedea et al (2009) found that, after adjusting for pre-treatment quality of life, there were no differences in quality of life following either LDRBT or EBRT.

Summary – What is the safety of low-dose-rate brachytherapy, compared with external beam radiotherapy, radical prostatectomy and active surveillance, as a treatment for localised prostate cancer?

Urinary side effects

A total of 13 comparative studies reported on the urinary related safety of low-dose-rate brachytherapy (LDRBT) compared with external beam radiotherapy (EBRT), radical prostatectomy (RP) and active surveillance (AS).

The incidence of urinary incontinence increases following treatment for prostate cancer. Urinary incontinence is more common among men treated with RP than LDRBT (Buron et al 2007; Ferrer et al 2008; Frank et al 2007; Giberti et al 2009; Guedea et al 2009; Smith et al 2010), a difference that may continue beyond 3 years. Incontinence was highest immediately following treatment and was reported in up to 68% of men treated with RP, 17% of men treated with LDRBT and 4% of men treated with EBRT. By 3 years following treatment, Smith et al (2010) reported incontinence in 12.3%, 5.4%, 2.7% and 3.4% of men treated with RP, LDRBT, EBRT and AS respectively. At baseline 6% of men managed with AS and 1% of age-matched non-prostate cancer men reported some urinary incontinence; therefore, some incontinence may be unrelated to treatment. Immediately following treatment, men treated with LDRBT may have higher rates of incontinence than men treated with EBRT (Pinkawa et al 2009); however, this difference did not endure (Ferrer et al 2008; Frank et al 2007; Guedea et al 2009; Pinkawa et al 2009; Smith et al 2010; Wei et al 2002).

Irritative or obstructive symptoms are more common following LDRBT than RP, with differences continuing beyond 12 months following treatment. In a randomised controlled trial, International Prostate Symptom Score (IPSS), a questionnaire specific for obstructive or irritative symptoms, was reported to be worse than baseline at 6 months and 1 year for men treated with LDRBT; however, no difference was found in irritative symptoms in men treated with RP. By 5 years, no difference was reported between the two treatments. Three studies reported worse irritative or obstructive symptoms following LDRBT compared with EBRT and two studies reported no difference. Importantly, one of the studies that reported no difference adjusted for baseline urinary symptoms, whereas those studies reporting a difference did not.

Urethral stricture may occur among men receiving any treatment for prostate cancer, although it may be more common following RP or LDRBT than EBRT. A randomised controlled trial reported urethral stricture in 2% of men treated with LDRBT and 6.5% of men treated with RP (Giberti et al 2009). However, the proportion of men developing urethral stricture following LDRBT varied among studies, from 0.15% to 14%. Consequently, it is difficult to draw conclusions regarding the likelihood of urethral stricture among patients treated with LDRBT in this review. Two studies reported urethral stricture among men treated with EBRT in nil and 2% of patients. Overall, among comparative studies, RP and LDRBT patients experienced urethral stricture more frequently than EBRT patients.

Urinary retention is more common following LDRBT than RP or EBRT. A randomised controlled trial reported urinary retention in 10% of men treated with

LDRBT and in nil men treated with RP (Giberti et al 2009). A retrospective cohort which matched patients on baseline characteristics (although not urinary function), reported catheterisation in 15% of men treated with LDRBT compared with nil men treated with EBRT (Pickles et al 2010).

Bowel side effects

A total of 15 comparative studies reported on the bowel-related safety of LDRBT compared with EBRT, RP and AS.

Bowel problems occur more frequently among men treated with LDRBT or EBRT than RP. Bowel motion frequency increased following LDRBT and EBRT; however, by 16 months, fewer men treated with LDRBT reported a moderate or big problem due to frequency (2%) than men treated with EBRT (12%).

Rectal bleeding and faecal incontinence increased in men treated with LDRBT more often than in men treated with RP (Buron et al 2007). No difference in bloody stools was noted between men treated with EBRT and LDRBT; however, different baseline rates of men reporting bloody stools may have disguised a greater increase in bloody stools among men treated with EBRT (Pinkawa et al 2009).

Painful bowel movements are more common in men treated with EBRT than LDRBT, both immediately after treatment and at a median of 16 months following treatment (Pinkawa et al 2009). Once again, findings were not adjusted for baseline symptoms and these results may be biased.

One large cohort study reported worse bowel function and bother (as measured by the UCLA-PCI questionnaire) among EBRT patients than LDRBT patients, and LDRBT patients reported worse bowel function and bother immediately after treatment than RP patients. In a multivariate analysis correcting for differences in baseline patient characteristics and including responses up to 2 years, treatment remained a significant predictor of both bowel function and bother.

Sexual dysfunction

A total of 10 comparative studies reported on sexual dysfunction following LDRBT and at least one of EBRT, RP and AS.

Erectile dysfunction is more common following RP than either EBRT or LDRBT. Men treated with nerve-sparing RP reported the lowest prevalence of erectile dysfunction[7] (15.6%) compared with men treated with LDRBT (19%), AS (27.3%) or EBRT (30.2%) (Smith et al 2010). Despite the baseline advantage, at 3 years more men treated with nerve-sparing RP reported impotence (67.9%) than men treated with LDRBT (36.4%) or AS (54.3%), and was equal to the proportion of men reporting impotence among men who received EBRT (67.9%). Men treated with non-nerve-sparing RP had the highest proportion of impotence (86.7%). Adjusting for age, baseline sexual function, comorbidities and demographic variables, men treated with both nerve-sparing and non-nerve-sparing RP experienced a far greater reduction in

[7] Defined by Smith et al (2010) as 'unable to obtain an erection sufficient for intercourse'.

sexual function as measured by the UCLA-PCI questionnaire than men treated with AS, EBRT and LDRBT.

This finding is almost unanimously supported by studies included in this review. A randomised controlled trial reports that by 5 years there is no difference in International Index of Erectile Function (IIEF) score between patients treated with LDRBT or RP (Giberti et al 2009). However, the quality of reporting in this study is poor, and it is not clear what proportion of men took part in this questionnaire or whether it included only men potent at baseline.

In studies comparing LDRBT and EBRT, only those that did not control for baseline functioning reported differences between the post-treatment sexual function of men treated with LDRBT and EBRT.

General health-related quality of life

A total of 10 comparative studies reported on health-related quality of life (HRQoL) following LDRBT and at least one of EBRT, RP and AS.

After adjusting for pre-treatment HRQoL, there were no differences in quality of life following RP, EBRT or LDRBT by 2 or 3 years following treatment (Guedea et al 2009; Smith et al 2010). Men treated with LDRBT may experience comparatively better HRQoL than men treated with RP for a short period of up to 3 months (Buron et al 2007; Ferrer et al 2008; Hashine et al 2008); however, not all studies were consistent and one study showed improved quality of life for men receiving RP beyond 6 months (Buron et al 2007).

Due to inconsistencies in studies and the use of different questionnaires, HRQoL is difficult to assess in this review. Of studies that reported a difference, they tended to favour LDRBT over RP *soon* after treatment. Given that RP patients may experience immediate symptoms, whereas LDRBT patients may not experience symptoms for some weeks or months following treatment, this finding fits a clinical model. Differences between LDRBT and EBRT were inconsistent between studies and cannot be assessed. Long-term HRQoL is not reliably reported and is unlikely to differ between treatments.

Is it effective?

The effectiveness of prostate cancer treatments has not been widely addressed in epidemiological and medical literature. To date, most investigations have been case series, focusing on one treatment without reference to an appropriate comparator. Such studies have therefore been limited to efficacy appraisal, not effectiveness, which requires at least two treatment options to be compared. The effectiveness of a given treatment will largely depend on a cancer's aggressiveness and stage of development as indicated by Gleason score, clinical stage and prostate specific antigen (PSA) level or kinetics. In the case of radiation therapies, including brachytherapy (BT) and external beam radiotherapy (EBRT), prescribed radiation dose and percentage of the prostate receiving the target dose are important factors that will influence patient outcomes. In the case of radical prostatectomy (RP), surgical technique will play a role. For all treatment modalities, effectiveness will depend on overall health (including comorbidities), age and other demographic variables associated with the patient. Studies investigating the effectiveness of prostate cancer treatments should take into account all these potential confounding factors; this assessment will consider the included studies' claims of effectiveness in light of these considerations.

The effectiveness of low-dose-rate (LDR) BT for the treatment of early prostate cancer was assessed relative to other treatments commonly used in Australia. Inclusion criteria for effectiveness were developed a priori but have been slightly adjusted to reflect the data available. Given that none of the eligible literature meet the requirement for comparative data with a minimum of 10-year patient health outcomes, this criterion was changed to allow studies with a minimum of 5-year outcomes to be included. The inclusion criteria separated patients into groups based on Gleason score ≤ 6, Gleason score 7 with a primary score of 3 and a secondary score of 4 (3+4), and Gleason score 7 with a primary score of 4 and a secondary score of 3 (4+3). Given that no included studies on effectiveness separated results by Gleason score according to these criteria, analysis of these groups has been combined. While Gleason score is less likely to affect safety outcomes, it is a strong prognostic marker for oncological and survival outcomes (Andren et al 2006; Burdick et al 2009; Stark et al 2009). This assessment is therefore limited by lack of data that differentiates effectiveness outcomes for patients on the basis of Gleason score. Most of the included studies have separated results by low-, intermediate- and high-risk prostate cancer. Generally, low- and intermediate-risk categories have correlated well with eligible patients as defined by our inclusion criteria, while patient populations falling within high-risk categories have not. For this reason, high-risk patients have not been considered for assessment.

Box 2 outlines the inclusion criteria for assessing the effectiveness of LDRBT as a treatment for low-risk prostate cancer. Primary measures of effectiveness considered for this review were cancer-specific survival, all-cause survival, clinical local and distant recurrence-free survival. Quality of life, often considered a function of effectiveness, has been addressed under safety considerations as the aim of treatment of low- or intermediate-risk prostate cancer is primarily to prolong the life of men who are often asymptomatic. Hence, detriments in quality of life are invariably linked to side effects from treatment. Secondary measures of effectiveness considered for this review were biochemical disease-free (bNED) survival, progression-free survival confirmed by bone scan, time to secondary therapy (including hormone therapy), length of hospital stay and

duration of treatment. Studies eligible for inclusion presented results on secondary effectiveness only in the form of bNED.

Box 2 Inclusion criteria for studies assessing the effectiveness of low-dose-rate brachytherapy for the treatment of localised prostate cancer

Research question	
1. Is low-dose-rate brachytherapy (LDRBT) as effective as, or more effective than, radical prostatectomy (RP)?	
2. Is low-dose-rate brachytherapy (LDRBT) as effective as, or more effective than, external beam radiotherapy (EBRT)?	
3. Is low-dose-rate brachytherapy (LDRBT) as effective as, or more effective than, active surveillance (AS)?	
Characteristics	**Criteria**
Population	Patients with early localised prostate cancer, defined as clinical stage T1 or T2, Gleason score ≤ 7 and a PSA ≤ 10 ng/mL. At least 85% of patients have met these criteria to be included, or patient groups have been stratified such that the eligible cohort component was available for analysis. Animal or in-vitro studies were not included.
Intervention	Studies involved LDRBT with iodine^{125} permanent implants. Studies involving palladium^{103} were excluded if more than 50% of the sample received ^{103}Pd, and patient outcomes were not stratified by radioactive source. Patients who received combined LDRBT with EBRT were not included in the analysis, and studies were excluded if data could not be separated.
Comparators	RP, EBRT and AS.
Outcome	*Primary outcomes:* Cancer-specific survival, all-cause survival, clinical local and distant recurrence-free survival. *Secondary outcomes:* Biochemical disease-free survival (bNED), progression-free survival confirmed by bone scan, time to secondary therapy and time to hormone therapy. Length of hospital stay, duration of treatment. ***All studies of effectiveness must present, at a minimum, 5-year outcomes.***[a]
Study design	Randomised or non-randomised controlled trials, cohort studies, case-control studies, registers, or systematic reviews of these study designs. Non-systematic reviews, abstracts, editorials, case reports and laboratory studies were excluded.
Search period	January 2000 – May 2010. Studies reviewed as part of the previous MSAC reviews were excluded unless new information could be extracted from the study due to the expanded eligibility criteria.
Language	Studies in languages other than English were only translated and included if they represented a higher level of evidence than was available in the English language evidence-base.

[a] Protocol amendment—originally specified 10-year outcomes.

A total of seven comparative studies were identified that met the selection criteria for assessing the effectiveness of LDRBT as a treatment for early prostate cancer. Of these studies, one was a randomised controlled trial of moderate quality (Giberti et al 2009). Five were retrospective cohort studies of moderate quality, of which one (Stokes 2000) was included in the previous MSAC assessment (1089). No additional information could be extracted despite the expanded eligibility criteria for this assessment, and therefore the study by Stokes et al (2000) was excluded. One included study (Vicini et al 2002) was an indirect comparison of multiple single-arm studies of poor quality. All studies are presented in Table 35, ranked by NHMRC level of evidence, then quality.

One randomised controlled trial (N=200) compared LDRBT and RP (Giberti et al 2009); one large population-based study (N=10,179) compared LDRBT, RP, EBRT, androgen deprivation therapy (ADT) and 'no treatment' (Zhou et al 2009); and three studies (Beyer & Brachman 2000; Pickles et al 2010; Wong et al 2009) (N=2,222, 278 and 853 respectively) compared LDRBT and EBRT. The large inter-institutional study (N=6,877) by Vicini et al (2009) compared six treatment modalities, but of these only LDRBT, EBRT, 3D-EBRT and RP were considered eligible (results for neutron therapy and high-

dose-rate BT were excluded from the analysis). No studies were available that compared LDRBT with AS.

Of the included studies, one presented results for primary effectiveness alone (Zhou et al 2009), two reported primary and secondary effectiveness outcomes (Pickles et al 2010; Vicini et al 2002), and three reported on secondary effectiveness alone (Beyer & Brachman 2000; Giberti et al 2009; Wong et al 2009). Specifically, the highest quality study by Zhou et al (2009) reported prostate cancer specific and all-cause survival at 7 years. Wong et al (2009) and Giberti et al (2009) reported 5-year bNED while Beyer and Brachman (2009) reported 5-year and 7-year bNED. Pickles et al (2010) reported number of deaths from prostate cancer, deaths from all other causes and bNED at 5 years, while the poor-quality study by Vicini et al (2002) reported overall survival and bNED at 5 years.

Primary effectiveness outcomes

The large, population-based study by Zhou et al (2009) was the only study with measures of effectiveness that included 'no treatment'[8] as a reference. The other comparators were RP, EBRT and ADT[9]. Data for a cohort of 10,179 men aged 65 years and older with incident prostate cancer were obtained from the records of Medicare, a cancer incidence surveillance system, and death certificates in the US. Of the total study population, 8,255 were diagnosed with localised disease and the remaining patients had distant metastases or cancer of unknown stage. Only results for patients with localised disease were considered for this review, as patients in higher risk groups did not satisfy the eligibility criteria and conclusions specific to low-risk prostate cancer treatment are not possible within population groups of unknown stage. The study methods allowed for treatment modalities administered as monotherapy or in combination, but only outcomes of monotherapy are included in this analysis.

Overall survival at 7 years for the localised disease group was estimated using Kaplan-Meier methods, and hazard ratios were calculated using Cox regression. The Kaplan-Meier analysis provided estimates of overall 7-year survival to be 89%, 81% and 71.7% for RP, LDRBT and EBRT respectively. Comparing the treatment modalities with 'no treatment' as the reference and controlling for age, race, tumour stage, Gleason score and pre-treatment comorbidity, hazard ratios for RP, LDRBT and EBRT were 0.32 (95% CI [0.25, 0.41]), 0.40 (95% CI [0.32, 0.52]) and 0.63 (95% CI [0.53, 0.75]) respectively. Compared with 'no treatment', this represented a significant difference for each treatment modality ($p<0.0001$), indicating that overall survival was 3, 2.5 and 1.6 times more likely for RP, LDRBT and EBRT patients respectively. Zhou et al (2009) did not directly compare LDRBT with the other treatments, but the confidence intervals for LDRBT and EBRT did not overlap, which suggests a significantly lower likelihood of dying from any cause among LDRBT patients than EBRT patients. Conversely, the confidence intervals

[8] Zhou et al (2009) indicated that the majority of patients in the 'no treatment' group were aged 75 years and older. It is likely that a large proportion of these patients were contraindicated for treatment, while some may have been AS patients. It is unlikely that the group as a whole constitutes an AS cohort. For this assessment, 'no treatment' is not considered as a comparator.

[9] For the purposes of this assessment, receiving ADT did not provide a basis for patient exclusion, but ADT monotherapy was not defined as an appropriate stand-alone comparator. Results for ADT, which Zhou and colleagues compared with the other treatment modalities, are therefore not considered.

for LDRBT and RP did overlap, suggesting no significant difference in overall survival between these two treatment options.

Prostate cancer specific survival (Kaplan-Meier) at 7 years was 97.9%, 96.6% and 94.2% for RP, LDRBT and EBRT respectively. Cox regression analysis, using 'no treatment' as the reference and adjustment for confounders, gave hazard ratios of 0.25 (95% CI [0.13, 0.48]) for RP, 0.45 (95% CI [0.23, 0.87]) for LDRBT and 0.66 (95% CI [0.41, 1.04]) for EBRT. There was a significant difference observed between the 'no treatment' and RP groups ($p<0.0001$), indicating that prostate cancer specific survival was four times more likely among the RP group than among patients who were not treated at all. The difference between the 'no treatment' and LDRBT groups was also significant ($p=0.018$), with survival slightly more than two times better among LDRBT patients. However, the confidence intervals suggest the possibility of no difference in prostate cancer survival among LDRBT patients compared with either RP or EBRT patients. In any event, given the width of these confidence intervals, the analysis is likely to be underpowered to show differences in prostate cancer specific survival.

Deaths from prostate cancer and non-prostate cancer causes were reported by Pickles et al (2010). One prostate cancer death was observed in each of the LDRBT and EBRT groups. Death from non-prostate cancer causes totalled 4 patients in the LDRBT group and 18 patients in the EBRT group ($p=0.001$) according to 8-year projections. With such small patient numbers, it is not possible to make conclusive judgements about effectiveness from these data.

Of the included studies on effectiveness, Vicini et al (2002) reported on the second largest cohort of patients (N=6877). However, the majority of these patients, who were accrued from seven centres, were ineligible for the purposes of this assessment on the basis of one or more prognostic criteria (PSA level, Gleason score and clinical stage). Data could be extracted for 1,698 eligible patients (clinical stage T1c/T2a, Gleason score ≤ 6 and PSA ≤ 10 ng/mL) from five centres that each presented results for patients treated with one modality. Overall survival for the LDRBT group treated at Centre 1 was 83%, but was not reported for the LDRBT group treated at Centre 2 or the 3D-EBRT group at Centre 3. For the EBRT and RP groups (Centres 4 and 5), overall survival was 85% and 97% respectively. Vicini et al (2002) is the lowest quality study in this evidence-base because, by comparing single-arm treatment groups between centres, the likelihood that confounding has been introduced into the analysis is high. Results cannot be adjusted for 'centre', as in most 'multicentre' studies, because the same treatment was not conducted in all centres. Although there was an attempt to stratify by prognostic factors, the authors acknowledged that confounding could only be addressed in a randomised controlled trial.

Table 11 Primary effectiveness outcomes comparing LDRBT, RP and EBRT

Study	Actuarial overall survival at 7 years (%)			
	LDRBT	RP	EBRT	p-value
Zhou et al (2009)	81.0	89.0	71.7	NR
	Actuarial disease-specific survival at 7 years (%)			
	LDRBT	RP	EBRT	p-value
Zhou et al (2009)	96.6	97.9	94.2	NR

LDRBT = low-dose-rate brachytherapy; EBRT = external beam radiotherapy; RP = radical prostatectomy; NR = not reported

Secondary effectiveness outcomes

Biochemical disease-free survival (bNED)

The randomised controlled trial by Giberti et al (2009) provided the highest level of evidence on secondary effectiveness outcomes. Five-year bNED was reported for 174 out of the 200 recruited low-risk prostate cancer patients; however, no definition of bNED was provided. A total of 26 patients (11 in the RP group and 15 in the LDRBT group) were lost to follow-up. Five-year bNED was 91% for RP and 91.7% for LDRBT.

Wong and colleagues (2009), in the highest quality cohort study reporting on secondary effectiveness outcomes, observed the 5-year bNED for 853 patients undergoing LDRBT or EBRT in two modalities—3D conformal and intensity modulated radiotherapy (IMRT). Biochemical failure was defined as an increase in PSA level of > 2 ng/mL above the nadir with no backdating (Phoenix definition). Data could only be extracted for low-risk patients who did not receive ADT (n=327). Five-year bNED was 92% for 3D-EBRT, 93% for IMRT and 97% for LDRBT, and no significant differences were observed.

A similar quality study by Beyer and Brachman (2000) compared 5-year and 7-year bNED for 1,527 EBRT and 695 LDRBT patients with 41.3 and 51.3 months of median follow-up respectively. Biochemical failure was defined as rising PSA (ASTRO definition), initiation of hormonal management, or PSA rising to 10 ng/mL or more despite the lack of three consecutive elevations.[10] Data were stratified according to baseline PSA. For the LDRBT group with PSA in the range 0–4 ng/mL, 5-year and 7-year bNED was 87% and 85%, respectively, while for the EBRT group, it was 90% in both cases. For the LDRBT group with PSA > 4–10 ng/mL, 5-year and 7 year bNED was 76% and 66%, respectively, while for the EBRT group, it was 74% and 69% respectively. There were no statistically significant differences between the treatment groups for either 5-year or 7-year biochemical disease-free survival.

The moderate-quality retrospective cohort study (N=278) by Pickles et al (2010) used a matched-pair design in patients treated with LDRBT and EBRT at a single Canadian institution. Patients in both groups, each comprising 139 patients, all had low- and intermediate-risk prostate cancer[11] and were analysed for 5-year bNED (Phoenix definition) using Kaplan-Meier methods. The patients in the intermediate-risk group who

[10] Some patients may have been classified as having failed on the basis of clinical evidence of disease.
[11] Low-risk patients were defined as PSA ≤ 10 ng/mL, T stage ≤ 2c and Gleason score < 7. Intermediate-risk patients were treated with LDRBT plus 6 months of ADT (3 months neoadjuvantly and 3 months concurrently with LDRBT) under the provision that they either had PSA ≤ 15 ng/mL with a Gleason score of ≤ 6 or Gleason score of 7 and PSA ≤ 10 ng/mL.

had a PSA > 10 ng/mL (but not > 15 ng/mL), were in all other respects eligible for inclusion and represented only 10% of the study sample. These patients were reported to have had localised disease (all patients were stage T2 or less), indicating good prognosis and eligibility for either LDRBT or EBRT. There were no significant differences between the groups in terms of any prognostic factors or baseline characteristics, with the exception that patients who received LDRBT were younger (median age 64 years) than those who received EBRT (median age 71 years). Within the low-risk group, 5-year bNED was 94% for LDRBT patients and 88% for EBRT patients ($p<0.001$; log-rank test). For the intermediate-risk group, 5-year bNED was 100% and 78% for the LDRBT and EBRT patients respectively ($p\leq0.016$). For low- and intermediate-risk groups overall, 5-year bNED was 95.2% for LDRBT and 84.7% for EBRT patients ($p<0.001$). Pickles et al (2010) reported that only 1 biochemical relapse was seen in the LDRBT group *beyond* 5 years, whereas 14 additional EBRT patients showed relapse for a projected failure rate of 50% at maximum follow-up. The PSA doubling time among those who experienced biochemical relapse was a median of 6 months in the LDRBT group and 24 months in the EBRT group ($p<0.001$).

In the poor-quality study by Vicini et al (2002), bNED was defined for radiotherapy patients as per ASTRO consensus and for surgical patients as any detectable level of PSA. Five-year bNED for the LDRBT groups treated at Centre 1 and Centre 2 was 82% and 89% respectively. Five-year bNED was 85% for the 3D-EBRT group (Centre 3), 71% for the EBRT group (Centre 4) and 97% for the RP group (Centre 5).

Table 12 Secondary effectiveness outcomes comparing LDRBT, RP and EBRT

Study		Freedom from biochemical recurrence at 5 years (%)			
		LDRBT	RP	EBRT	p-value
Giberti et al (2009)		91.7	91.0	-	NR
Wong et al (2009)		97	-	92 / 93[1]	0.298
Beyer and Brachman (2000)					
PSA, ng/mL	0-4	87	-	90	0.47[2]
	>4-10	76	-	74	0.76[2]
Pickles et al (2010)					
Low risk		94	-	88	<0.001
Intermediate risk		100	-	78	≤0.016
Overall		95.2	-	84.7	<0.001
Vicini et al (2002)		82 / 89[3]	97	71 / 85[4]	NR
Study		**Freedom from biochemical recurrence at 7 years (%)**			
		LDRBT	**RP**	**EBRT**	**p-value**
Beyer and Brachman (2000)					
PSA, ng/mL	0-4	85	-	90	0.47[2]
	>4-10	66	-	69	0.76[2]

[1] the external beam radiotherapy is separated into 3D-CRT / IMRT; [2] p-value is for between-group comparison for both time-points; [3] centre 1 / centre 2; [4] EBRT / 3D-EBRT

LDRBT = low-dose-rate brachytherapy; EBRT = external beam radiotherapy; RP = radical prostatectomy; IMRT = intensity modulated radiotherapy; PSA = prostate specific antigen; NR = not reported

Summary – What is the effectiveness of low-dose-rate brachytherapy, compared with external beam radiotherapy, radical prostatectomy and active surveillance, as a treatment for localised prostate cancer?

Primary effectiveness outcomes

A total of three comparative studies reported on primary effectiveness outcomes for low-dose-rate brachytherapy (LDRBT) (Pickles et al 2010; Vicini et al 2002; Zhou et al 2009).

Overall survival after treatment was assessed in two studies. The highest quality study (Zhou et al 2009) did not directly compare LDRBT with the other treatment modalities (external beam radiotherapy (EBRT) and radical prostatectomy (RP)), but rather indirectly via comparison with a 'no treatment' group. Overall survival results suggest that LDRBT patients are not likely to fare any worse than EBRT patients and have similar overall survival to RP patients. The other study (Vicini et al 2002) was of poor quality and presented data on primary effectiveness for three out of four eligible treatments—RP, LDRBT and EBRT. With no testing for statistical significance and questionable conclusions on the part of the authors, the point estimates provide inadequate evidence for either a difference or similarity between the treatments.

One study (Pickles et al 2010) reported on prostate cancer specific death and death from all causes; however, this represented a small number of deaths among the total number of patients after a follow-up of less than 10 years. This similarly provides no conclusive evidence about the superiority of either treatment used (LDRBT or EBRT).

Secondary effectiveness outcomes

A total of five comparative studies reported on secondary effectiveness outcomes for LDRBT (Beyer & Brachman 2000; Giberti et al 2009; Pickles et al 2010; Vicini et al 2002; Wong et al 2009). All but one of these presented results for 5-year freedom from biochemical recurrence (bNED). In addition, Beyer & Brachman (2000) also presented 7-year bNED.

Studies that presented bNED were all of moderate quality and the majority (Beyer & Brachman 2000; Giberti et al 2009; Wong et al 2009) found no differences in outcomes between LDRBT or EBRT (RP was not assessed in these studies).

Pickles et al (2010) found that bNED was 10% greater among LDRBT patients than among EBRT patients.

The poor-quality study by Vicini et al (2002) was inadequate to affect the weight of evidence, indicating that there is no difference in bNED for LDRBT or EBRT. This was the only study to report on bNED for RP.

What are the economic considerations?

In its assessment of a new service, the MSAC is required to consider not only the safety and comparative effectiveness of the service but also the comparative cost and cost-effectiveness of the service. The purpose of the economic evaluation is to inform the decision made by the MSAC on the additional costs and additional gains (health or other socially relevant outcomes) of the proposed service over the comparator when used in the Australian healthcare context. This is to ensure that society's ultimately scarce resources are allocated to those activities from which it will get the most value.

When undertaking economic analysis, initially a systematic review (and/or meta-analysis) is produced to determine whether there is evidence that the intervention is comparatively effective (see Effectiveness section page 55). An economic analysis is only undertaken if there is evidence that the procedure under consideration is as effective as, or more effective than, the designated comparator(s). Due to the limited comparative evidence, it is not possible to definitively conclude whether low-dose-rate (LDR) ^{125}I brachytherapy (BT) for localised prostate cancer is as effective as, or more effective than, radical prostatectomy (RP), external beam radiotherapy (EBRT) or active surveillance (AS). Therefore, only a cost analysis of the expenditures associated with the new procedure relative to the comparative procedures was conducted.

The cost data cover all non-trivial health system resources; indirect costs, also known as productivity costs, were not considered. All cost data were acquired from 2008–09 (round 13) public and private estimated Australian Refined Diagnosis Related Groups (AR-DRG) cost report, July 2010 Medicare Benefits Schedule, Pharmaceutical Benefits Scheme (effective 1 September 2010) and the August 2010 version of the prostheses list.

The costing exercise conducted is not intended for fee scheduling purposes, and is not a recommendation for funding at these levels.

Existing literature

Studies addressing the cost-effectiveness of LDR ^{125}I BT for localised prostate cancer were assessed for inclusion in this report according to the criteria outlined in Box 3.

Box 3 Inclusion criteria for studies assessing the cost-effectiveness of low-dose-rate brachytherapy for the treatment of localised prostate cancer

Research question	
1. What is the cost-effectiveness of low-dose-rate brachytherapy (LDRBT) compared with radical prostatectomy (RP)?	
2. What is the cost-effectiveness of low-dose-rate brachytherapy (LDRBT) compared with external beam radiotherapy (EBRT)?	
3. What is the cost-effectiveness of low-dose-rate brachytherapy (LDRBT) compared with active surveillance (AS) (no initial treatment)?	
Characteristics	**Criteria**
Population	Patients with early localised prostate cancer, defined as clinical stage T1 or T2, Gleason score ≤ 7 and a PSA ≤ 10 ng/mL. At least 85% of patients have met these criteria to be included, or patient groups were stratified such that the eligible cohort component was available for analysis. Animal or in-vitro studies were not included.
Intervention	Studies involve LDRBT with iodine^{125} permanent implants. Studies involving palladium^{103} were excluded if more than 50% of the sample receives ^{103}Pd, and patient outcomes were not stratified by radioactive source. Patients who received combined LDRBT with EBRT were not included in the analysis, and studies were excluded if data could not be separated.
Comparators	Gleason ≤ 6: RP, EBRT and AS.
	Gleason = 7: RP and EBRT.
Outcome	Incremental cost-effectiveness ratio, cost per life year gained, cost per quality adjusted life year gained, cost.
Study design	Economic trial-based studies, modeling studies and costing studies.
Search period	January 2000 to May 2010. Studies reviewed as part of the previous MSAC reviews were excluded unless new information coiuld be extracted from the study due to the increased eligibility criteria.
Language	Studies in languages other than English were only translated and included if they represented a higher level of evidence than was available in the English language evidence-base.

One health technology assessment (HTA) combining the findings of three systematic reviews, and three comparative studies, were identified that met the inclusion criteria for assessing the economic considerations of LDRBT as a treatment for early prostate cancer. These studies are presented in Table 36 and are listed in order of NHMRC level of evidence and then quality. One review combining data from three systematic reviews compared the incremental cost-effectiveness ratio of LDRBT, RP, 3D-CRT, IMRT and AS (Ollendorf et al 2009a). Three studies compared costs incurred in the delivery of LDRBT with those incurred in the delivery of RP (Buron et al 2007; Ciezki et al 2000; Kohan et al 2000). The study profiles of all included studies are listed in Appendix J.

Cost comparisons

Three studies of moderate-quality[12] presented the costs of LDRBT compared with the costs of RP. One multicentre study of moderate quality was undertaken in France (Buron et al 2007), and the remaining two single-centre studies, one of moderate quality (Ciezki et al 2000) and one of poor quality (Kohan et al 2000), were undertaken in the US. Two studies reported that, while the structure of costs differed between RP and LDRBT, mean overall costs were similar. Buron et al (2007) reported that mean hospital costs after 24 months were 7,463 euros for RP and 7,427 euros for LDRBT (adjusted to 2001 costs). Immediately following treatment, RP was, on average, 687 euros less expensive than

[12] The quality of these studies was assessed using the checklist produced by Downs and Black (1998)—this was deemed more appropriate than the checklist developed by Drummond and Jefferson (1996), which contains criteria specific for economic evaluations and is unsuited for simple cost comparison studies.

LDRBT, with the costs of hospitalisation largely balancing the costs of the BT seeds. Over the following 2 years, LDRBT incurred fewer hospital costs and approximately the same outpatient costs. Interestingly, the production losses reported by Buron were markedly different comparing LDRBT with RP. By 2 years following treatment, mean costs due to loss of productivity among working patients were 620 euros for LDRBT and 3,678 euros for RP patients. Kohan et al (2000) reported that mean total charges by 1 year following treatment were US$13,904.60 for RP and US$13,886.00 for LDRBT. In contrast with Buron et al (2007), Kohan et al (2000) reported that mean post-treatment charges were higher for LDRBT (US$2,285.20) than for RP (US$1,007.20).

The final study by Ciezki et al (2000) did not consider post-operative costs and concluded that perioperative LDRBT costs were 1.85 and 2.05 times greater than RP costs for pre-planned and intra-operative planned techniques respectively.

While the practice of LDRBT and RP in all three studies appears similar to that in Australia, the overall costs are unlikely to be transferable to the Australian setting.

Cost–utility analysis

One HTA was identified that compared the cost-effectiveness of LDRBT, RP, EBRT and AS (Ollendorf et al 2009a). This report compiles evidence from three systematic reviews addressing the safety, effectiveness and cost-effectiveness of RP and AS (Ollendorf et al 2009b), LDRBT and proton-beam therapy (Ollendorf et al 2008), and intensity modulated radiotherapy (IMRT) (Pearson et al 2007). All three systematic reviews were undertaken by the Institute for Clinical and Economic Review (ICER). The reviews addressed the benefits and harms of treatments for localised, low-risk prostate cancer. Low-risk disease was defined as clinical stage T1–T2a, Gleason score ≤ 6 and PSA < 10 ng/mL. The reviews required only a preponderance of patients who met the criteria for low-risk disease and hence many included studies would have been excluded in this review. For LDRBT only one comparative study was included, which has been identified by the search criteria for this review and included in relevant sections. All other studies involving LDRBT were case series (with the exception of one randomised controlled trial comparing ^{125}I and ^{103}Pd isotopes for LDRBT).

Applying the Drummond et al (1996) checklist to the report on the comparative effectiveness and value of all treatments reveals a high-quality economic evaluation. However, the quality of systematic reviews on which the rates of side effects were based was moderate to poor, using the checklist for systematic reviews developed by NHMRC (NHMRC 2000). While the search strategies and inclusion criteria appear to have been appropriately developed and applied, no quality assessment appears to have been done, reported study characteristics are inadequate and sources of bias or confounding in the results were only briefly addressed. Ostensibly, the purpose of the systematic review was the creation of an economic model, and greater care with reporting outcomes from case series might appear gratuitous. It is therefore perhaps unfair to criticise the reviews regarding their reporting, in particular when the evidence-base was of such poor quality to begin with.

The modelled economic analysis was performed with a Markov model with transition probabilities and health state utilities sourced from existing literature. Costs for primary treatments and for treating side effects were sourced from published studies, interviews with clinicians and US Medicare current procedural terminology codes, and adjusted to 2007 US dollars. Side effects from treatments were sourced largely from the combined ICER systematic reviews.

Several important assumptions were made within the model:

- All treatment modalities are equally effective with respect to survival. Patients have equal likelihood of biochemical recurrence, disease progression and cancer-specific death regardless of which primary treatment they choose. Treatments will differ with respect to side effect profiles only.
- No patient receives adjuvant therapy (all patients are treated with one modality only).
- Men under AS will be treated with RP or IMRT following PSA progression, Gleason upgrading or patient decision. After 5, 10 and 15 years of AS, respectively, 28%, 45% and 54% of men will have received definitive treatment.
- Following a period of AS there is no detrimental effect on survival in men who receive primary treatment (the likelihood of disease progression reverts to that of all other men who have received the treatment).

Transition probabilities, costs and utilities were sampled using probabilistic sensitivity analysis. The base-case results for incremental quality adjusted life years (QALYs), incremental costs and incremental cost per QALY for 65-year-old men is presented in Table 13.

Table 13 Total and incremental quality adjusted life years, total and incremental cost, and incremental cost-effectiveness ratio (cost/QALY) of active surveillance, low-dose-rate brachytherapy and intensity modulated radiotherapy compared with radical prostatectomy for the treatment of localised prostate cancer

Strategy	QALYs	Incremental QALYs	Cost	Incremental cost	Cost/QALY
AS	8.97	1.15	$30,422	$2,074	$1,803
LDRBT	8.12	0.30	$25,484	-$2,864	N/A[a]
IMRT	8.09	0.27	$37,861	$9,513	$35,233
RP	7.82	Reference	$28,348	Reference	Reference

Note: Incremental values are calculated relative to radical prostatectomy.
QALYs = quality adjusted life years; AS = active surveillance; LDRBT = low-dose-rate brachytherapy; IMRT = intensity modulated radiotherapy; RP = radical prostatectomy
[a] Strategy is less costly and more effective than reference strategy.

Under the assumption of equal survival among treatments, the differences in QALYs are entirely due to the side effect profiles and their assigned utilities. In the base-case result, LDRBT achieved 0.3 more QALYs than RP. As LDRBT is also less expensive than RP, it represents a cost-saving in this model. IMRT, which also achieves a QALY advantage over RP, is more expensive than RP. The extra 3.2 months of perfect health achieved by choosing IMRT over RP would cost an additional US$9,513, or US$35,233 per additional QALY gained.

The model has some limitations. First, the rates of treatment side effects were estimated from the three aforementioned systematic reviews, which were largely based on poor-quality, non-comparative studies. Second, the small overall differences in QALYs between the treatments will make even slight differences in treatment effectiveness important in calculating overall QALYs gained from the treatments. While the assumption of equivalent survival of the included treatments is necessary because of the

lack of comparative and randomised studies, undetected differences in effectiveness will largely invalidate the model's results. Third, the QALYs are calculated using broad categories of treatment-related side effects (ie urinary side effects, gastrointestinal side effects and sexual dysfunction). Given that treatments may have different side effect profiles, the side effects that resulted in the overall loss in QALYs will be different between treatments. It is likely that some patients will be more averse to some side effects than others, and their quality of life (QoL) will be impacted to a different extent depending upon the side effect profile. It may be that a man who values his potency would suffer greater loss of QoL following RP, while a man who is more likely to experience urinary retention and require frequent catheterisation may prefer to avoid radiation treatments. Finally, estimated costs are drawn from the US healthcare system and are likely to be different in Australia. Given how closely the four treatment strategies are with respect to QoL outcomes, the model will be sensitive to relatively minor differences in costs.

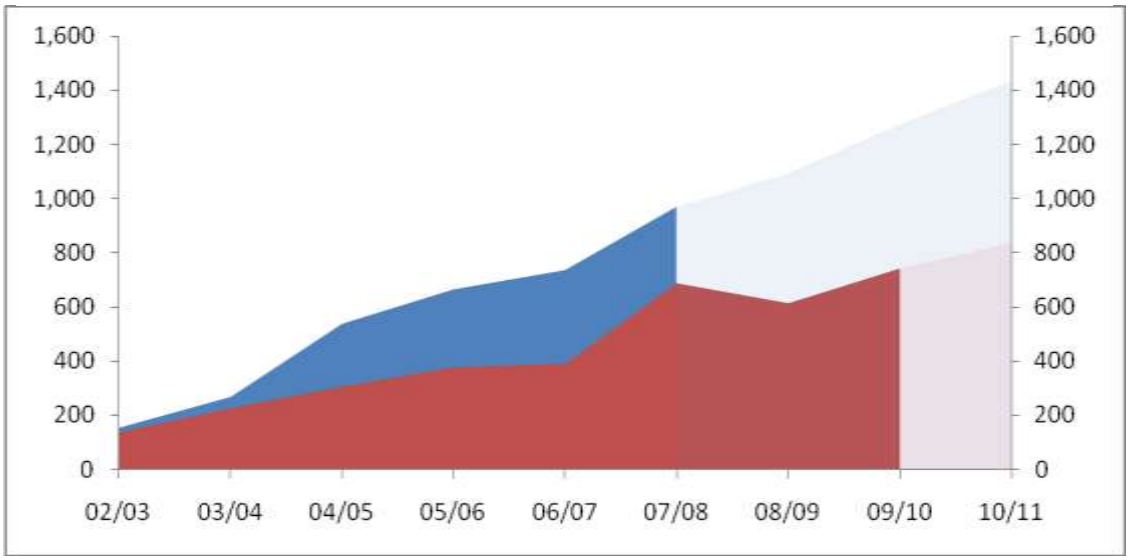
Financial impact analysis

Likely number of procedures in a typical year

The number of low-dose-rate (LDR) ^{125}I brachytherapy (BT) procedures for the treatment of localised prostate cancer per year is likely to rise. In the 2007–08 financial year, 968 procedures were undertaken in Australia, as recorded by the Australian Institute of Health and Welfare (AIHW). At the same time there were 687 claims for Medicare reimbursement. The disparity of nearly 300 treatments represents the proportion of procedures that were undertaken within the public hospital system. Assuming a linear trend using data from the 2005–06 financial year onward, by the end of the 2010 financial year roughly 1,400 procedures would take place in either the public or private sector, as shown in Figure 5.

This projection is crude. First, it fails to take into account the trend of diagnoses occurring in increasingly younger men with earlier stage or lower grade disease who would be eligible for LDRBT. It also assumes that there will be no great change in community preference for comparative treatments, in particular active surveillance (AS). If trends mirror those in the US, LDRBT is likely to become a treatment of choice for men with low-risk disease (Cooperberg et al 2004). However, the projected number of procedures will be constrained by the number of radiation oncology departments with the equipment and training able to offer LDRBT; it is therefore unlikely that numbers will increase sharply.

Figure 5 Actual and projected numbers of low-dose-rate brachytherapy procedures (item number 15338) by financial year



Source: Medicare Item Reports (2010) for item number 15338 (in red), available online (https://www.medicareaustralia.gov.au/statistics/mbs_item.shtml); AIHW procedural cubes for 15338 (in blue), available online (http://www.aihw.gov.au/hospitals/datacubes/datacube_proc.cfm)

While the use of LDRBT has been estimated at approximately 1,400 procedures per year, the use of other treatment modalities is more uncertain. Both radical prostatectomy (RP) and external beam radiotherapy (EBRT) may be used in men with disease that would not be suitable for treatment with LDRBT; therefore, utilisation numbers from the AIHW will be imprecise. The use of AS in Australia is also uncertain. In an Australian

population-based cohort study (Smith et al 2010), 20% of men diagnosed with Gleason 6 prostate cancer were reported to have opted for AS; however, this study was based on data from 2000–02 and rates of AS may have altered substantially since.

Likely number of eligible patients in a typical year

No reliable Australian source has been found that reports on the likely distribution of Gleason scores among men diagnosed with localised prostate cancer. However, a publication characterising the risk profile of prostate cancer across the US using 2004–05 data from the Surveillance, Epidemiology and End Results (SEER) database (Shao et al 2009) reported that approximately 55% of all patients diagnosed with Gleason ≤ 7 disease have Gleason scores of 2–6, and 45% have Gleason scores of 7.

For simplicity, and because more accurate figures are unavailable, 5,000 incident diagnoses of localised disease with Gleason score ≤ 7 each year in Australia (as previously estimated in potential utilisation on page 12) are assumed to be eligible for LDRBT. This number is based on calculations using 2006 data; changes in prostate cancer incidence will affect costing estimates.

Of these cases, 55% are assumed to be of Gleason score 2–6 and 45% are Gleason score 7. Initially, overall costs will be estimated on the premise that one-third of patients will select each of the active treatments. In a subsequent analysis involving AS, it will be assumed that 20% of patients with Gleason ≤ 6 prostate cancer select AS, with the remaining 80% distributed equally among LDRBT, RP and EBRT. AS will not be costed for men diagnosed with Gleason 7 prostate cancer, one-third of whom will be assumed to select each of the active treatments.

It should be noted that this analysis will only reflect the costs of implementing LDRBT, EBRT, RP and AS in the population of men who are eligible for LDRBT, and will not reflect the cost of treating all men diagnosed with prostate cancer.

Unit costs

The work-up for each of ^{125}I LDRBT, EBRT, RP and AS is similar, with a few exceptions. It is assumed that all patients will be seen by a urologist regardless of the final treatment decision. Patients undergoing treatments involving radiation will also see a radiation oncologist. Due to the low-risk profile of patients with clinically localised cancer with PSA ≤ 10 ng/mL and Gleason score ≤ 6, staging with whole-body bone scan and computerised tomography scan will not be costed. It is likely that, in practice, a proportion of such low-risk patients will undergo these staging procedures, but this will vary from practice to practice. For men with Gleason score 7 disease, staging scans will be costed for all treatments. In addition, all LDRBT patients will undertake a urine flow study to ensure they are not at high risk for post-implant urinary retention. It has been assumed that luteinising hormone releasing hormone analogues (LHRHa) will be used only for treatments involving radiation. Men receiving LDRBT are assumed to receive one 3-month course of LHRHa in one-third of cases for prostate volume reduction. Among men receiving EBRT, LHRHa is not used for cytoreduction, as it is in LDRBT, but has been shown to confer a survival advantage in men who take it concurrently with treatment (D'Amico et al 2004). There appears to be no benefit for such adjuvant use of hormones among men with low-risk disease (Zeliadt et al 2006); LHRHa have therefore been costed only among men with Gleason 7 disease, and then only for 6 months in one-third of cases. However, the adjuvant use of LHRHa may be less common among men with Gleason scores of 3+4=7 than among men with Gleason scores of 4+3=7; and the

costing is therefore likely to be an overestimation of the costs involved in treating men with 3+4=7 disease. The services accessed are presented in Table 14.

Table 14 Services associated with low-dose-rate ^{125}I brachytherapy, external beam radiotherapy, radical prostatectomy and active surveillance for localised prostate cancer

Component	Low-dose-rate brachytherapy	External beam radiotherapy	Radical prostatectomy	Active surveillance[a]
Initial urologist consult	X	X	X	X
Initial radiation oncologist consult	X	X		
Whole-body radionuclide scan[b]	X	X	X	X
Computerised tomography scan[b]	X	X	X	X
Pre-anaesthetic consult	X		X	
Radiotherapy planning	X	X		
Hospitalisation	X[c]		X	
Radiotherapy procedure	X	X		
Surgical procedure			X	
Pathology[d]			X	X
Blood transfusion			X	
Medications	X	X	X	
Follow-up urologist consult	X	X	X	X
Follow-up radiation oncologist consult	X	X		
Follow-up PSA test	X	X	X	X
Re-biopsy				X

[a] A high proportion of men on active surveillance will progress to treatment; [b] Medicare data reveals that whole-body bone scan and computerised tomography (CT) scan were accessed in the same 18-month period as a brachytherapy procedure in more than 60% and almost 100% of cases respectively. However, the indication for the scans is not certain (whether they were used specifically for prostate cancer staging). To reflect best practice, whole-body bone scan and CT scan will only be costed for men with Gleason 7 disease (expert opinion); [c] Only 16.5% of brachytherapy procedures in the 2007–08 financial year were flagged as same day or overnight procedures; the remainder are assumed to have taken place as inpatient procedures; [d] Pathology associated with radical prostatectomy is the examination of the entire prostate, whereas for active surveillance it represents the examination of subsequent biopsy material.

Hospitalisation will be required for both LDRBT and RP. Therefore, those procedures undertaken while in a hospital will be reflected in the total average charge per AR-DRG estimate (with the exception of the cost of the BT seeds). There is no AR-DRG specific to the LDRBT procedure and the average costs associated with the broad AR-DRG involving BT admissions will be heavily skewed by the costs of other, more complex procedures undertaken within that same AR-DRG in the public hospital system. Given that the brief admission for the LDRBT procedure is likely to be uncomplicated, an AR-DRG with a short average length of stay has been sourced from the private sector and applied to both public and private costings. The rationale for taking the average cost per separation from the private sector is that the cost does not involve the salaries of clinicians, which may be substantial in public sector average separation costs. For the costing of LDRBT, the salaries of public sector clinicians will then be approximated by using the MBS reimbursement. The AR-DRG chosen to reflect a simple overnight stay is L08B – Urethral procedures-CC, which has an average length of stay of 1.43 days and an average cost of separation of $1,577 in the private sector. This decision will render the overall costs of LDRBT identical between the two sectors, with the only difference being the source of funding.

The AR-DRG linked to retropubic RP is M01Z – Major Male Pelvic Procedures, and has been used for both public and private costings. The cost per separation for AR-DRG M01Z differs markedly between the public and private sectors. This is primarily due to the differing accounting methods that produce the cost per separation figure, which in the private sector does not include professional fees, pathology or pharmaceutical costs. However, even when incorporating these fees, the private cost per separation remains substantially less than the public cost per separation. It is unlikely that this difference resembles a true difference in the overall costs, but rather a mixture of confounding elements. Cost per separation is largely estimated from modelled data in the private sector (Australian Government Department of Health and Ageing 2009b), which will result in the underestimation of costs involved in complex AR-DRG categories. Admissions in public institutions tend to be more complex in nature and patients may have a greater number of comorbidities. In addition, out-of-pocket expenses charged to patients for professional fees and hospital costs in the private sector are also unrecorded. In a recent publication by the Productivity Commission (Productivity Commission 2010), cost per separation was estimated by summing the costs incurred in each admission for both public and private hospitals. For AR-DRG M01Z, the Commission's experimental cost estimates for public and private hospitals were almost identical ($15,175 in public vs $14,996 in private). In light of this, the true cost of RP is more likely to be reflected by the overall costs incurred in the public sector. However, costs in the private sector have also been presented because the proportion of costs borne by the MBS and the state/territory governments differs between public and private hospitals.

It is important to note that the cost of RP is based on the open technique. There are no data providing an accurate proportion of men who undergo robot-assisted laparoscopic prostatectomy in Australia, and this procedure was estimated as $4,262 more costly by the May 2006 MSAC report (Medical Services Advisory Committee 2006). Therefore, the costs of RP will be underestimated.

EBRT and AS procedures are performed in an outpatient setting and the cost implications to either the MBS or the Australian Government will not vary significantly between the public and private sectors.

AS is not universally practised across Australia; however, the Urological Society of Australian and New Zealand (USANZ) has recently signed up to participate in the Prospective Validation of Active Surveillance (PRIAS) study, and endorses the use of AS among men with low-risk, localised prostate cancer. Despite this, there is no Australian-based recommendation regarding disease monitoring while on AS, nor what constitutes a trigger for active treatment. Therefore, AS protocols must be sourced internationally.

In costing AS as an option for the management of localised prostate cancer, we are primarily interested in the proportions of men who remain on AS and those who opt for active treatment. This is highly variable and most men choose to move to active treatment rather than move following changes in PSA level or Gleason score on repeat biopsy (Dall'Era et al 2008; van den Bergh et al 2009). However, this decision represents a real-life observation and will be costed over that of the ideal situation in which men remain on AS until prompted into active treatment as a consequence of changes to their disease status. Due to the uncertainty surrounding the assumptions made for AS as well as its reliance upon the costings of LDRBT, RP and EBRT, it will be addressed following an analysis involving only active treatments. Data sources and assumptions for the costing are outlined in the AS section.

Costs associated with treating prostate cancer are presented in Table 15. A summary of costs, grouped by work-up/staging, procedure and consumables for patients in the private sector is presented in Table 16. Table 17 includes the minimum costs of monitoring a patient following treatment, assuming that no patient suffers disease recurrence or progression. Individual unit costs, descriptions of the service and rationale for their inclusion are addressed at length in Table 37 (BT), Table 38 (EBRT), Table 39 (RP) and Table 40 (AS), located in Appendix M.

Table 15 Costs associated with the treatment of localised prostate cancer

Component	Low-dose-rate brachytherapy (Table 37)	External beam radiotherapy (Table 38)	Radical prostatectomy (Table 39)
Work-up and staging			
Initial urologist consult	$80.85 (MBS item 104)	$80.85 (MBS item 104)	$80.85 (MBS item 104)
Initial radiation oncologist consult	$80.85 (MBS item 104)	$80.85 (MBS item 104)	
Whole-body bone scan	*$479.80 (MBS item 61421)*	*$479.80 (MBS item 61421)*	*$479.80 (MBS item 61421)*
Computerised tomography scan[a]	*$365.03 (MBS items 56507 or 56409)*	*$365.03 (MBS items 56507 or 56409)*	*$365.03 (MBS items 56507 or 56409)*
Urine flow study	$26.05 (MBS item 11900)		
Pre-anaesthetic consult	$40.60 (MBS item 17610)		$40.60 (MBS item 17610)
Procedure			
Planning and simulation	$592.90 (MBS item 15539)	$1,681.70 (MBS items 15550 *and* 15562)	
Procedure	$1,871.15 (MBS items 37220 *and* 15338)	$7,392.60 (MBS items 15248 *and* 15263)b	$1,807.14 (MBS items 37210 *and* 51303)[c]
Anaesthesia	$205.70 (MBS items 21973 *and* 23063)		$448.80 (MBS items 20845 *and* 23114)
Additional imaging	$453.07 (MBS items 55603 *and* 15513 *and* 60509 or 60506)[d]	$2,834.20 (MBS item 15705)2	
Hospitalisation (private / public)	$1,577 / $1577[e]		$8,685 / $13874[f]
Pathology			$470.00 (MBS item 72838)
Consumables and medications			
^{125}I brachytherapy seeds	$7,000 (Prostheses list code ON003)		
Luteinising hormone releasing hormone analogue	$369.59 (PBS code 8093Y)	*$739.17 (PBS code 8093Y)*	
Cross-matching and blood			$150.43 (MBS items 65099 and 13706 + $329 per unit of blood)[g]
Gleason 6 patients[h]			
Total cost (private / public)	**$12,297.75**	**$12,070.20**	**$11,682.82 / $13,995.45**
Gleason 7 patients			
Total cost (private / public)	**$13,142.58**	**$13,654.20**	**$12,527.65 / $14,840.28**

Items in italics are costed for patients with Gleason 7 disease only (Advisory Panel);[a] Based on Medicare data, 56507 and 56409 are used equally often; therefore, an average cost of these two items has been presented; [b] Based on a 37fraction/5 field treatment technique with daily verification imaging; [c] A surgical assistant is present at 100% of procedures and claims one-fifth of the principal surgeon's fee; [d] A transrectal ultrasound is required for the brachytherapy procedure and, in two-thirds of cases, fluoroscopy is used (either 60509 or 60506); [e] Based on AR-DRG L08B – Urethral procedures-CC private sector data used—see discussion for rationale (2008–09 Cost Report); [f] Based on AR-DRG M01Z – Major male pelvic procedures for public and private separations (2008–09 Cost Report); [g] Assume all radical prostatectomy patients are cross-matched and 5% of patients require 2 units of blood, $329 per unit (Medical Services Advisory Committee 2006); [h] Gleason score ≤ 6.

Table 16 Costs of treating localised prostate cancer in the private sector—by Gleason score

Gleason score ≤ 6

Component	Low-dose-rate brachytherapy	External beam radiotherapy	Radical prostatectomy
Work-up and staging	**$228.35**	**$161.70**	**$121.45**
Procedure	**$4,699.82**	**$11,908.50**	**$11,410.94**
Consumables and medications	**$7,369.59**	**$0.00**	**$150.43**
Total costs	**$12,297.75**	**$12,070.20**	**$11,682.82**

Gleason score 7

Component	Low-dose-rate brachytherapy	External beam radiotherapy	Radical prostatectomy
Work-up and staging	**$1,073.18**	**$1,006.53**	**$966.28**
Procedure	**$4,699.82**	**$11,908.50**	**$11,410.94**
Consumables and medications	**$7,369.59**	**$739.17**	**$150.43**
Total costs	**$13,142.58**	**$13,654.20**	**$12,527.65**

Table 17 Cost of follow-up and cumulative costs of treatment for localised prostate cancer in the private sector—for patients with Gleason score ≤ 6[a]

			Cost per year (instances)	
Component	Source	Unit cost	Years 1–3	Year 4+
Urologist subsequent visit	**MBS item 105**	**$40.60**	**$81.20 (2)**	**$0.00 (0)**
GP visit	**MBS item 411**	**$40.40**	**$0.00 (0)**	**$40.40 (1)**
PSA test	**MBS item 66656**	**$20.30**	**$40.60 (2)**	**$20.30 (1)**

Cumulative costs per year[b]	Treatment	Year 1	Year 2	Year 3	Year 5	Year 10
Follow-up alone[c]	**-**	**$121.80**	**$243.60**	**$365.40**	**$486.80**	**$790.30**
Follow-up alone[d]	**-**	**$118.72**	**$231.50**	**$338.64**	**$437.55**	**$644.67**
Low-dose-rate brachytherapy[d]	**$12,298**	**$12,416**	**$12,529**	**$12,636**	**$12,735**	**$12,942**
Radiotherapy[d]	**$12,070**	**$12,189**	**$12,302**	**$12,409**	**$12,508**	**$12,715**
Radical prostatectomy[d]	**$11,683**	**$11,802**	**$11,914**	**$12,021**	**$12,120**	**$12,327**

[a] For cumulative costs to treat Gleason 7 patients, add $844.83 to the overall cost of brachytherapy and radical prostatectomy and $1,584.00 to the overall cost of external beam radiotherapy; [b] The costs associated with follow-up assume that no patient has a recurrence or requires further treatment. As there is no evidence that any one treatment is more effective than another, the added costs for further treatment will be incurred equally across all treatments; [c] undiscounted costs; [d] discounted costs (at 5% per annum with half cycle correction)

Costs to the Australian Government

The Australian Government is responsible for payment of the rebate on items from the MBS. As ^{125}I LDRBT is performed in a hospital facility, the rebate would be 75% of the schedule fee for a private hospital facility. Many of the services leading up to the provision of LDRBT occur in an outpatient setting, during which time the MBS will reimburse 85% of the overall cost. The Australian Government is also responsible for the difference between the cost of pharmaceutical benefit items and the amount borne by the consumer. The costs associated with LDRBT, EBRT and RP as borne by the MBS, other government agencies (federal or state/territory), and the patient or their private insurance fund are outlined in Table 18 for a private hospital and Table 19 a public hospital.

Table 18 Costs and source of funding for the treatment of one man with localised prostate cancer in a private setting with 10 years follow-up

Source of funds	Low-dose-rate brachytherapy	External beam radiotherapy	Radical prostatectomy
Costs borne by MBS[a]			
Outpatient attendances and procedures	$194.10	$10,259.67	$103.23
In-hospital procedures	$2,401.40	$0.00	$1,804.78
Follow-up	$578.53	$578.53	$578.53
Gleason 7 only	$718.11	$718.11	$718.11
Cost borne by other government agencies			
Hospitalisation	$0.00	$0.00	$0.00
PBS / other	$367.79	$0.00	$0.00
Gleason 7 only	$0.00	$735.57	$0.00
Cost borne by patient / private insurance[a]			
Outpatient attendances and procedures	$34.25	$1,810.53	$18.22
In-hospital procedures (inc. seeds)	$9,300.21	$0.00	$9,756.59
Follow-up	$66.15	$66.15	$66.15
Gleason 7 only	$126.72	$130.32	$126.72
Total costs			
Gleason ≤ 6	**$13,088.05**	**$12,860.50**	**$12,473.12**
Gleason 7	**$13,932.88**	**$14,444.50**	**$13,317.95**

[a] Based on MBS reimbursement of 85% of the fee for benefit for out-of-hospital procedures and MBS reimbursement of 75% of the fee for benefit for in-hospital procedures.

Table 19 Costs and source of funding for the treatment of one man with localised prostate cancer in a public setting with 10 years follow-up

Source of funds	Low-dose-rate brachytherapy	External beam radiotherapy	Radical prostatectomy
Costs borne by MBS[a]			
Outpatient attendances and procedures	$194.10	$10,259.67	$103.23
In-hospital procedures	$2,401.40	$0.00	$0.00
Follow-up	$578.53	$578.53	$578.53
Gleason 7 only	$718.11	$718.11	$718.11
Cost borne by other government agencies			
Hospitalisation	$2,298.00	$0.00	$13,874.00
PBS / other	$7,367.79	$0.00	$0.00
Gleason 7 only	$0.00	$735.57	$0.00
Cost borne by patient / private insurance[a]			
Outpatient attendances and procedures	$34.25	$1,810.53[c]	$18.22
In-hospital procedures (inc. seeds)	$1.80[b]	$0.00	$0.00
Follow-up	$66.15	$66.15	$66.15
Gleason 7 only	$126.72	$130.32	$126.72
Total costs			
Total Gleason ≤ 6	**$13,088.05**	**$12,860.50**	**$14,785.75**
Total Gleason 7	**$13,932.88**	**$14,444.50**	**$15,630.58**

[a] Based on MBS reimbursement of 85% of the fee for benefit for out-of-hospital procedures and MBS reimbursement of 75% of the fee for benefit for in-hospital procedures; [b] The cost of in-hospital procedures is based on the MBS reimbursement as well as the private hospital average cost per separation for AR-DRG L08B; 100% of the MBS fee (proposed to reflect clinicians' fees) will be absorbed by the government and will not be borne by the patient; [c] While this figure represents 15% of the MBS fee for external beam radiotherapy, patients in a public setting will not be expected to bear these costs, which will be absorbed by the state/territory government.

Despite differences in services used, the three curative treatments differ only slightly in overall cost. The costs borne by the MBS, however, differ substantially, with EBRT costing between $10,974 and $11,692, compared with all other treatments costing between $817 (RP in a public setting for Gleason ≤ 6 disease) and $4,028 (LDRBT in a public or private setting for Gleason 7 disease). This is primarily because EBRT is performed as an outpatient procedure whereas RP is performed in an inpatient setting and the cost of BT seeds (the largest single expense of LDRBT) is not reimbursed by the MBS.

Treating men with Gleason 7 disease increases the cost to the MBS by approximately $720 per patient, which is more than one-fifth of the total MBS cost for either LDRBT or RP. This increased cost is across all treatments, and is made up by an increased use of staging scans (whole-body bone scan and computerised tomography scan). It is important to note that different practices exist across institutions and between specialists regarding the use of staging scans among prostate cancer patients. It is likely that a proportion of men with Gleason ≤ 6 prostate cancer, despite their low risk of adverse findings, will also receive staging scans, resulting in an increased cost to the MBS.

Cost to the Australian healthcare system

The total cost of LDRBT, EBRT and RP to the Australian healthcare system includes payments made through the MBS; the costs of hospitalisation, medications and the radioactive seeds required for LDRBT; payments made by private insurers; and co-payments made by patients. As presented in Table 18, the overall cost to the Australian healthcare system for treatments delivered in the private sector differs marginally among the three modalities. For patients with Gleason ≤ 6 disease, LDRBT costs approximately $13,088, EBRT approximately $12,861 and RP approximately $12,473. For patients with Gleason 7 disease, both LDRBT and RP increase in overall cost by $845 and EBRT (which has been costed to involve the addition of 6 months of LHRHa for one-third of patients) increases in overall cost by $1,584. The costs of LDRBT and EBRT are identical in the public sector, but RP increases in cost to $14,786 for patients with Gleason ≤ 6 disease and $15,631 for patients with Gleason 7 disease. This increase (of $2,313) is likely an estimation error based on the different cost per separation in the public and private sectors for the AR-DRG M01Z. As previously mentioned, AR-DRGs from the public and private sectors are not directly comparable, and it is likely that the private sector AR-DRG cost per separation used in this model slightly underestimates the true cost associated with RP.

The single largest expenditure for LDRBT is the implanted radioactive seeds. In the public healthcare sector, this cost is borne by some state/territory governments by arrangement with individual hospitals, which may limit the provision of LDRBT in the public system.

Costs associated with continued monitoring following treatment will be identical across treatments and will be in the range $60–120 per year. Costs of follow-up will increase markedly upon disease recurrence following LDRBT, RP and EBRT and will include secondary treatments such as salvage radiotherapy or hormone therapy. Therefore, the costs presented only apply to those men who receive initial treatment and do not experience disease recurrence or require further treatment.

Total cost for provision of services to the entire population

To cost the provision of LDRBT to the entire eligible population, costs from the private and public healthcare sectors have been combined, assuming that 70% of all LDRBT procedures and 75% of all RPs occur in the private sector. These figures are based on the disparity between the AIHW clearing house figures (all procedures performed in Australia) and those services that attracted a Medicare benefit (private procedures only). The proportion of men treated in the public or private sectors will not affect the costs associated with the provision of EBRT. It is also assumed that 55% of all men treated will have Gleason ≤ 6 prostate cancer.

All costs have been discounted at 5% per annum using a half-cycle correction.

Two scenarios have been costed. In ***scenario 1*** the annual costs to the MBS, other governmental agencies (state/territory governments or Pharmaceutical Benefits Scheme (PBS)), and patient or private insurer have been estimated if one-third of all 5,000 men considered to be eligible for LDRBT are equally likely to select either LDRBT, EBRT or RP. The results of scenario 1 are shown in Table 20. This estimate represents the overall discounted costs to the Australian healthcare system in the absence of AS.

In ***scenario 2*** it is assumed that 20% of men diagnosed with Gleason ≤ 6 disease are initially managed with AS, with the remainder of patients (ie 80% of men with Gleason scores of ≤ 6 and all men with Gleason scores of 7) being distributed equally among LDRBT, EBRT and RP. This estimate represents the overall costs to the Australian healthcare system of treating men with localised prostate cancer including the best approximation of AS utilisation in Australia. Due to the more gradual accrual of costs among men who opt for AS, discounting future costs will reduce the overall cost of the AS protocol. Discounting will have little effect on the costs associated with immediate treatment due to the relatively small costs incurred during the follow-up period.

Table 20 Scenario 1: Total costs borne by MBS, other governmental bodies, and patient or private insurance over a 10-year period based on one-third of all men electing each treatment

	LDRBT	EBRT	RP	LDRBT vs EBRT	LDRBT vs RP	EBRT vs RP
MBS	$5,828,622	$18,602,239	$3,930,815	–$12,773,617	$1,897,807	$14,671,424
Other government	$5,262,185	$551,680	$5,780,833	$4,710,505	–$518,648	–$5,229,153
Patient / private insurer	$11,113,527	$3,225,540	$12,431,393	$7,887,987	–$1,317,866	–$9,205,853
Total	$22,204,334	$22,379,458	$22,143,041	–$175,124	$61,293	$236,417

In scenario 1 (Table 20) it is assumed that one-third of all patients considered to be eligible for ^{125}I LDRBT opt for the each of the available treatments (excluding AS). Assuming that 55% of these patients have Gleason ≤ 6 disease, the total cost to the MBS would be $28.362 million. Other governmental bodies, such as state/territory governments or the federal government through the PBS, are responsible for $11.595 million, and patients or private insurers are responsible for $26.770 million. The overall cost to the Australian healthcare system would be $66.727 million.

In comparative terms, treating one-third of all patients with LDRBT would cost the MBS, on average, $12.774 million less than treating the same men with EBRT. However, the overall cost of treating men with LDRBT is only marginally ($175,000) less than treating

them with EBRT. Therefore, the cost saving to the MBS is due entirely to redistribution of costs from the MBS and toward the state/territory governments (in the public sector) and private insurers or patients (in the private sector).

One cost associated with both LDRBT and EBRT is the use of LHRHa. In men treated with LDRBT, LHRHa is primarily used to reduce the overall size of the prostate gland, and it has been assumed to apply in one-third of cases. In men treated with EBRT, LHRHa is used only among those who are deemed at a higher risk of cancer spread. For this analysis, one-third of patients with a Gleason score of 7 have been assumed to have received 6 months of adjuvant LHRHa. The use of LHRHa in both LDRBT and EBRT varies between practices. Given that the use of LHRHa represents a substantial cost ($1,108.76 per 3-month dose), small variations in utilisation patterns may result in large overall impacts in cost.

Treating one-third of all eligible patients with LDRBT would cost the MBS approximately $1.898 million more than if the same patients were treated with RP. The disparity in this cost to the MBS is largely because public patients in public hospitals are not eligible for a Medicare benefit for RP. In contrast, if delivered as an outpatient procedure in a public hospital, LDRBT (like EBRT) may be eligible for a Medicare benefit. However, the difference in total costs is small, with LDRBT being $61,293 more costly than RP.

Costs to the Australian Government and healthcare system of active surveillance

AS for many (if not most) men represents deferred treatment, with studies reporting between 26% and 69% of men under AS opting for active treatment within 10 years (Roemeling et al 2007; Soloway et al 2010; van den Bergh et al 2009). Therefore, the costs associated with AS are largely dependent upon the costs of the treatments that men ultimately select.

The cost of treating 20% of men with Gleason ≤ 6 prostate cancer considered to be eligible for LDRBT with AS is presented in Table 22. To generate the costing, several assumptions are required:

1. For the base case, it was assumed that 57% of men would opt for active treatment by 10 years (van den Bergh et al 2009). The rate at which men opt for active treatment is not linear and assuming a linear trend (ie 5.7% per year) would have implications for overall cost when discounted. More precisely, the transition from AS to active treatment occurs more rapidly over the first few years and then decreases over time. Figure 6 shows the actuarial freedom from treatment from four studies involving AS and one hypothetical actuarial freedom-from-treatment graph based on 50% more men opting for treatment each year than observed in the van den Bergh et al (2009) study. These results have been taken from tables from the respective publications when available, or extracted from the Kaplan-Meier plots directly. While the use of actual survival data may improve the accuracy of costing, allowing a more rapid transition to treatment soon after diagnosis, it is not without risk. Sudden changes in failure rates from year to year most likely represent fluctuations specific to the study and may not represent the true transition to treatment in the wider population. However, small fluctuations in transition rates will have only a small impact on overall cost.

2. It is assumed that one-third of men who opt for active treatment are treated with LDRBT, one-third with EBRT and one-third with RP. In a cohort study by van den

Bergh et al (2009), roughly half of the men choosing treatment following AS opted for RP, half chose EBRT and less than 10% chose hormone therapy. The choice of treatment following a period of AS may be limited by several factors: upgrading on repeat biopsy or increases in PSA may render a man unsuitable for LDRBT; and older men who choose active treatment may be unsuitable for surgery. However, for this costing, it is assumed that men will remain eligible for all three treatments (BT, EBRT and RP) and that one-third will choose each modality.

3. No man will progress to incurable disease while on AS. While this assumption may be tenuous, the likelihood of significant disease progression is low if men are monitored correctly.

4. Men on AS will receive a PSA test and digital rectal examination (requiring a visit to a urologist or general practitioner) four times per year. In a recent review Klotz (2010) recommends a PSA test every 3 months for the first 2 years, then every 6 months thereafter.

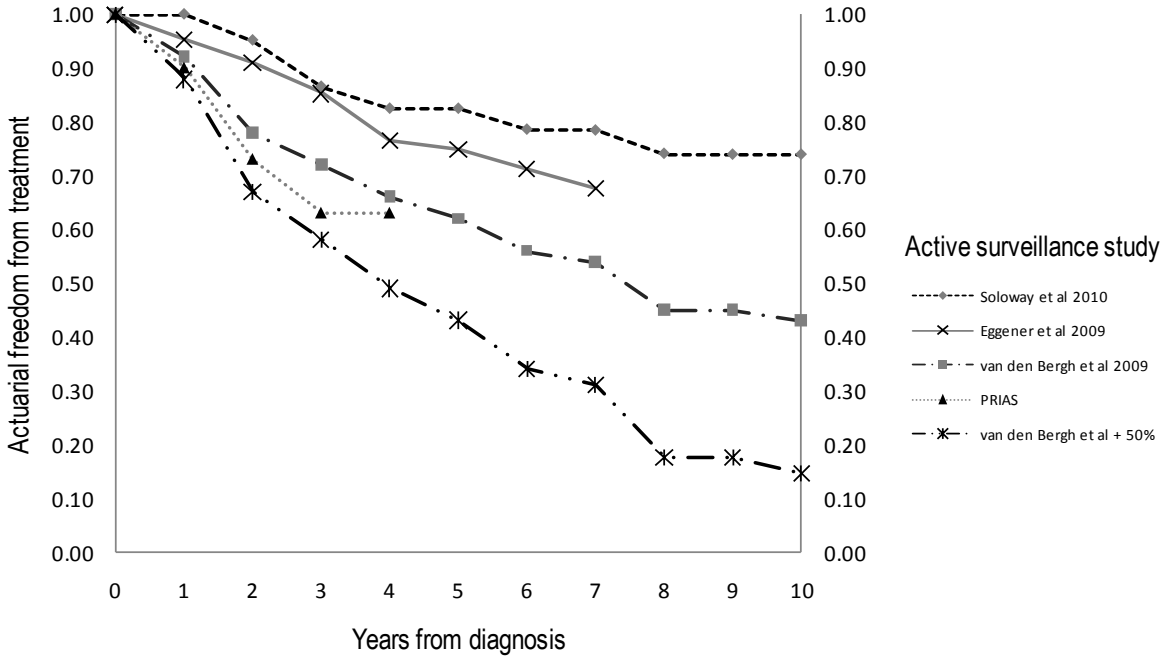
5. One confirmatory biopsy will be performed for every man who remains on AS in the first year after diagnosis and a subsequent biopsy will be costed for every man who decides on active treatment. While some clinicians have recommended regular biopsies for men on AS (Klotz et al 2010; Al Otaibi et al 2008), in reality far fewer men receive regular biopsies and the assumption of two additional biopsies for every man who progresses to treatment exceeds the observed biopsy rate in some cohorts (van den Bergh et al 2009).

6. One transrectal ultrasound (TRUS) will be performed every year for men who remain on AS, although this has not been costed for the first year, during which all men receive a TRUS guided biopsy.

7. The cost of immediate treatment (including all costs except for follow-up) has not been discounted. While using a half-cycle correction warrants the discounting of costs in the first year, treatments are assumed to occur in the first 6 months and therefore would not attract discounting. Due to the difficulty in disaggregating the costs associated with AS as well as uncertainty as to when they would be incurred, costs associated with AS have not been discounted in the first year. This will result in a minor overestimation of the overall costs ascribed to AS (less than 0.5%).

8. Follow-up costs have been simplified from variable costs following active treatment (reducing over time) to a constant cost of $121.80 per year. This will have little impact on the overall cost of treatments.

Figure 6 Transition to and from active surveillance to treatment over 10 years



Sources: Soloway et al (2010), Eggener et al (2009), van den Bergh et al (2009), van den Bergh et al (2010) (PRIAS study)
PRIAS (Prostate cancer Research International: Active Surveillance) registered at http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1718

Individual costs incurred while on AS are presented in Table 21. Active treatment is assumed to occur as per Table 18 and Table 19, with 70% of men receiving LDRBT and 75% receiving RP in a private setting. It is assumed that 55% of men eligible for LDRBT will have Gleason ≤ 6 disease. For the base case, 20% of men with Gleason ≤ 6 prostate cancer will opt for AS.

Table 21 Costs associated with active surveillance for localised prostate cancer

Component	Active surveillance (see Table 40)
Year 1	
Initial urologist consult	$80.85 (MBS item 104)
Initial radiation oncologist consult	$80.85 (MBS item 104)
PSA test (x4)	$81.20 (unit cost $20.30 MBS item 66656)
Re-biopsy	$584.85 (MBS items 37219, 55600 and 72827)
Urologist follow-up (x4)	$162.40 (unit cost $40.60 MBS item 105)
Years 2–10 while on active surveillance	
PSA test (x4)	$81.20 (unit cost $20.30 MBS item 66656)
Urologist follow-up (x4)	$162.40 (unit cost $40.60 MBS item 105)
Transrectal ultrasound	$109.10 (MBS item 55600)
On transition to active treatment	
Re-biopsy	$584.85 (MBS items 37219, 55600 and 72827)
Active treatment costs[a]	
Low-dose-rate brachytherapy	$12,297.75
External beam radiotherapy	$12,070.20
Radical prostatectomy	$12,260.98
Follow-up costs	
Combined costs per year[b]	$121.80 (Table 17)

[a] Treatment costs are based on the per patient costs from Table 18 and Table 19 combined, assuming that 70% of men receive LDRBT and 75% receive RP in the private sector. Discounted follow-up costs ($644.67) have been excluded from the costs of active treatment and will be costed separately depending upon the length of time a patient is followed; [b] The cost of follow-up in analyses presented for active treatments reduces to $60.70 per year from year 4 onwards, but for simplicity it has been assumed to remain fixed at the initial rate of $121.80 for all patients regardless of time since treatment.

Unlike immediate treatment, in which most of the costs are incurred immediately, the costs associated with AS are deferred. Therefore, while the overall costs of AS may approach those of active treatment, discounting the costs will markedly alter the overall cost of the AS option. A discounting rate of 5% per year, using a half-cycle correction, has been applied for all analyses.

The annual costs of treating 5,000 men with LDRBT, EBRT, RP or AS are presented in Table 22. This scenario represents the best estimate of the total cost of treating all men considered to be eligible for LDRBT in 2010, and involves initiating AS for 20% of all patients with Gleason ≤ 6 prostate cancer, with 57% eventually receiving active treatment over the 10-year costing period.

Table 22 Scenario 2: Total discounted costs borne by MBS, Australian healthcare system, and patient or private insurance over a 10-year period for treating 5,000 men, with 20% of Gleason ≤ 6 men opting for active surveillance[1]

	LDRBT	EBRT	RP	AS	Total
MBS	$5,589,800	$16,958,319	$3,900,752	$2,485,521	$28,934,392
Other government	$4,683,345	$551,680	$5,144,942	$579,952	$10,959,918
Patient / private insurer	$10,015,356	$2,995,345	$11,188,257	$1,590,987	$25,789,944
Total	$20,288,501	$20,505,344	$20,233,950	$4,656,460	$65,684,255

[1] The costs of LDRBT are the weighted average costs associated with treating men 70% in private and 30% in public. The costs of RP are the weighted average costs associated with treating men 75% in private and 25% in public. The costs of EBRT will not change from the public and private systems. The costs of all treatments, including AS, are discounted at 5% per year with half-cycle correction. The cost of AS is not discounted in the first year.

The overall annual cost to the MBS of treating men according to scenario 2 is $28.934 million. The cost to the MBS of managing 20% of men diagnosed with Gleason ≤ 6 prostate cancer with AS is not insubstantial, for two reasons. First, the monitoring of men while on AS is entirely performed in an outpatient setting; therefore, 85% of the MBS fee will be borne by Medicare. Secondly, scenario 2 assumes that one-third of men who ultimately receive active treatment will select EBRT, which is more than 80% funded by the MBS.

The overall discounted annual cost to the Australian healthcare system of treating 5,000 men according to scenario 2 is $65.684 million. While 11% of men are initially managed with AS, this component of management is responsible for only 7% of the total costs.

The acceptability of AS to patients and clinicians will affect both the uptake of and persistence with AS. It remains unclear how acceptable AS is within Australian culture. For this reason, a study with a high rate of patients moving from AS into active treatment was used for the base case cost estimate (van den Bergh et al 2009), which in turn will result in a conservative estimate as presented in Table 22. The figure of 20% AS among men diagnosed with Gleason ≤ 6 prostate cancer is sourced from data gathered between October 2000 and October 2002 (Smith et al 2010), which predates the initiation of several international AS studies and may underestimate its current utilisation in the community. However, the data also largely predate the introduction of LDRBT and robotic prostatectomy, two treatments that may appeal to younger men and impact on the proportions of men opting for AS. To represent the uncertainty surrounding the proportion of men opting for and persisting with AS, overall costs to the Australian healthcare system associated with different rates of participation in AS and treatment-free survival are presented in Table 23.

Table 23 Total cost to the Australian healthcare system of treating 5,000 men with localised prostate cancer for different rates of active surveillance (AS) and different likelihoods of opting out of AS

	Uptake of active surveillance in Australia			
Source of treatment-free survival rates[a]	0%	20%	30%	50%
Soloway et al (2010)		$64,180,846	$62,137,719	$58,051,467
van den Bergh et al (2009)	$68,267,098[b]	***$65,684,255***[c]	$64,392,833	$61,809,990
van den Bergh et al (2009) + 50%		$67,076,049	$66,480,525	$65,289,476

[a] Soloway et al (2010) published a Kaplan-Meier treatment-free survival curve. The extracted 5-year and 10-year treatment-free survival rates were 82.5% and 74.0% respectively. Van den Bergh et al (2009) published tabled data of yearly actuarial rates of treatment-free survival with 5-year and 10-year rates of 62% and 43%. To calculate a higher rate of men opting out of AS, a hypothetical treatment-free survival rate was calculated to represent 50% more men choosing active treatment than in the van den Bergh study each year. This hypothetical situation results in a 5-year and 10-year treatment-free survival of 43% and 14.5% respectively. Figure 6 displays the actuarial treatment-free survival curves sourced from Soloway et al 2010 and van den Bergh et al 2009, and the hypothetical treatment-free survival rate used in this costing; [b]The disparity between the cost of no AS in this table and the total cost in scenario 1 is due to the simplification of the follow-up costing—resulting in a fixed follow-up cost of $121.80 per year; [c] The base case (scenario 2) is presented in Table 22.

Irrespective of the proportion of men remaining under AS, the overall discounted cost of managing men with AS is less than the cost of immediate treatment. If 20% of men opt for AS, and 74% of those men remain under AS for 10 years, as was reported in the Soloway et al 2010 study, the total discounted cost to the Australian healthcare system would be over $4 million less than if no men opted for AS and $1.5 million less than if men opted out of AS at the base-case rate (57%) by 10 years.

It is important to recognise that the overall costs of an AS protocol will be sensitive to the ongoing costs of monitoring patients. More frequent biopsies or scans will markedly increase the cost of managing men with AS; however, monitoring costs would need to increase in the base case between four- and five-fold over those used in this analysis before AS would become more costly than immediate active treatment.

Discussion

Is it safe?

The safety of low-dose-rate brachytherapy (LDRBT) for the treatment of localised prostate cancer was assessed according to four criteria: the effect on urinary function; the effect on bowel function; the effect on sexual function; and the effect on general health-related quality of life. A total of 14, 16, 11 and 11 comparative studies (level II – III-3 intervention evidence) were identified that evaluated the urinary side effects, bowel side effects, sexual dysfunction and detriments in general health-related quality of life, respectively, following LDRBT compared with at least one of: radical prostatectomy (RP), external beam radiotherapy (EBRT) and active surveillance (AS).

Urinary side effects

The most common urinary side effect following LDRBT is a transient increase in irritative or obstructive symptoms. In all included studies comparing LDRBT and RP, urinary irritation was greater following LDRBT than RP. Two studies comparing LDRBT and EBRT reported worse urinary irritation following LDRBT and two reported no difference. Most studies reported irritative symptoms using mean results from questionnaires, and precise rates of symptoms could not be extracted.

Urinary incontinence was less common among men receiving LDRBT and EBRT than men receiving RP. Immediately following treatment, urinary incontinence was reported by up to 68.4% of men receiving RP and up to 17% of men receiving LDRBT. By 3 years, differences between the treatments were more modest, with up to 12.3% of men receiving RP and 7% of men receiving LDRBT continuing to experience urinary incontinence. Urinary incontinence following EBRT and in men receiving AS was infrequent, with incontinence at 3 years in up to 2.7% for EBRT and 3.4%t for AS. Studies did not distinguish between types of incontinence and it is possible that 'incontinence' following radiation treatments may represent urgency rather than lack of control.

Urinary retention was more frequent following LDRBT than RP. The proportion of men with urinary retention reported by comparative studies varied between 9% and 15% among men treated with LDRBT, and zero and 4% among men receiving RP. One study reported no urinary retention among EBRT patients and no study reported urinary retention rates in men undergoing AS.

Urethral stricture was reported in between 0.15% and 14% of men receiving LDRBT, in 6.5% of men receiving RP and in 2% of men receiving EBRT. Due to the small number of eligible studies reporting on urethral stricture following treatment, it is difficult to conclude whether there is a difference between treatments. Rates of urethral stricture following LDRBT, EBRT, RP and AS could not be assessed in this review.

In studies that used validated questionnaires to report urinary function, urinary bother or scores that combined the two, the differences were usually small or questionable, or data were presented in such a way as to make assessment difficult. In one study that showed a large difference in urinary function between LDRBT and RP (Hashine et al 2008), the

questionnaire was primarily designed to capture detriments in urinary-related quality of life associated with incontinence, and was likely to be less sensitive to irritative and obstructive urinary symptoms. Both urinary function and urinary bother scores slightly favoured radiation treatments over surgery, although the magnitude of difference could not be ascertained in this review due to the variability of the results and the incompatibility of the questionnaires used in different studies. Only one study included men managed with AS (Smith et al 2010), and a proportion of the men received active treatment during the follow-up period; therefore, AS could not be assessed in this review.

Bowel side effects

Bowel side effects were poorly reported by most comparative studies that primarily used either a patient-reported questionnaire score or a clinician-reported side effects scale to represent overall detriments in bowel function following treatment. Bowel side effects results varied across studies, with some studies reporting a difference between treatments and others showing minimal or no difference. Importantly, no study reported worse bowel symptoms following RP compared with LDRBT, and only one study reported worse bowel symptoms following LDRBT compared with EBRT.

Worsening of faecal incontinence was reported in 2% and 8.9% of men at 2 years following RP and LDRBT respectively. Worsening of rectal bleeding occurred in 15.1% of men receiving LDRBT, and no man receiving RP reported a worsening of rectal bleeding, at 2 years. Bloody stools were reported by 17% of men compared with 12% of men at a mean of 16 months following EBRT and LDRBT respectively.

Of studies reporting on bowel function questionnaire components or clinician-rated side effects, men receiving RP tended to have better bowel function following treatment than men receiving LDRBT, who in turn had better bowel function than men receiving EBRT. In a multivariate analysis, adjusting for baseline characteristics, the largest comparative study reported that treatment was significantly associated with bowel function up to 2 years. The overall modelled differences in bowel function were small and of questionable clinical importance. However, the modelling technique may be insensitive to large disparities in bowel function early after treatment, with UCLA-PCI bowel function scores of 75, 68 and 60 at 3 months following treatment with RP, LDRBT and EBRT respectively. The same study also reported a significant difference in UCLA-PCI bowel bother scores, with LDRBT an average of 7.1 points higher (less bother) than EBRT, and RP an average of 9.4 points higher than EBRT, on a scale of 0–100 and adjusting for baseline characteristics. A large Australian cohort study also adjusted for baseline characteristics and found worse bowel function following treatment in men receiving EBRT, but not RP or LDRBT, compared with an age-matched cohort without prostate cancer. Interestingly, bother from bowel symptoms increased for all treatments although more severely for men receiving EBRT.

Without the reporting of incidences of specific bowel side effects such as incontinence, pain, bloody stools, constipation and diarrhoea, it is difficult to interpret differences in bowel symptom scores. It is likely that men receiving LDRBT experience more bowel side effects and bother associated with side effects than men receiving RP. It is also likely that men receiving LDRBT experience fewer bowel side effects and bother than men receiving EBRT. However, several studies report no difference and one study reports fewer side effects following EBRT than LDRBT. Only one study regards men managed with AS but, as a proportion of the men crossed to active treatment in the follow-up

period, an accurate assessment of the bowel side effects of AS could not be undertaken in this review.

Sexual dysfunction

Perhaps more than urinary or bowel function, erectile function varies manifestly with age. An Australian survey found that 11.9% of men aged 50–59 years were unable to achieve an erection adequate for intercourse, and this increased markedly to 42.3% at age 60–69 years and 64.2% for men aged 70–79 years (Pinnock et al 1999). For studies comparing the erectile function of two groups, it is therefore vital that the groups are of a similar age. Merely excluding patients who were not potent before treatment from analysis will not remove the bias associated with the natural onset of erectile impotence with age if groups are not comparable at baseline. In a non-randomised setting, an additional source of bias when considering erectile function as an outcome may be that patients most interested in preserving sexual function will choose treatments that are advertised as offering higher rates of post-treatment potency. This will tend to exaggerate the potency rates for treatments selected by potent men who may be highly motivated to undertake erectile rehabilitation following treatment. The post-treatment use of phosphodiesterase type 5 (PDE5) inhibitors will also be a strong source of bias if use is not equal between groups.

In comparative studies the proportion of men reporting post-treatment potency among those who were potent before treatment varied from 67% to 95.7% following LDRBT and 51% to 68.8% following EBRT. At 18 months following RP, 83.3% of men who were sexually active before treatment reported a diminished ability to achieve or maintain an erection, compared with 45.8% of men who received LDRBT.

Sexual function, as reported by patient questionnaires, was consistently greater among men following LDRBT or EBRT than among men following RP, with the exception of two studies that showed no difference. In a large Australian cohort, adjusting for baseline function, demographics and comorbidities, sexual function was poorer following either nerve-sparing or non-nerve-sparing RP than EBRT or LDRBT. In studies comparing sexual function following EBRT and LDRBT, either no difference was reported or baseline function was not accounted for, introducing substantial bias into the results. Only one study compared LDRBT with AS and found no difference at 3 years after adjusting for age, baseline sexual function, comorbidities and demographics. However, a proportion of the men managed with AS crossed to active treatment during the follow-up period and this will strongly confound the results. Sexual function following AS could not be adequately assessed by this review.

There are conflicting reports regarding sexual bother following treatments, with one study reporting greater bother among men receiving RP than LDRBT after 12 months, and one study reporting no difference at a mean of 4 and 3.5 years following RP and LDRBT respectively. This suggests that bother may reduce over time.

General health-related quality of life

Health-related quality of life following treatment for prostate cancer is likely to reflect impairments due to side effects of treatments. Localised prostate cancer is largely asymptomatic; therefore, treatments are aimed at eradicating prostate cancer and not at

improving the quality of life of a man with prostate cancer. In the longer term differences in health-related quality of life (HRQoL) will be contingent upon treatment effectiveness, with men who have recurrent disease reporting lower utility than those who remain disease free. For low-risk prostate cancer, differences in effectiveness are unlikely to manifest in the short term, and hence this review has considered HRQoL to be a facet of safety rather than effectiveness.

More than half of all comparative studies considered eligible for this review reported on general HRQoL using a patient questionnaire. Unfortunately, the instrument used to measure HRQoL varied among the trials. Four different questionnaires (SF-36, EORTC QLQ-C30, FACT-G and FACT-P) and several methods of presenting the results as either global measures or compartmentalised measures of the physical, mental or a myriad of other components make inter-study comparison of the results difficult.

Overall, there are mixed results when comparing quality of life following treatment in men receiving LDRBT with those receiving RP or EBRT. In most cases there were no differences or only very small differences of questionable clinical relevance among all three treatments.

Comparing LDRBT with RP, in studies reporting on quality of life very early after treatment, LDRBT consistently performed better than RP. However, HRQoL was no different in most studies beyond 6 months. Interestingly, two studies reported greater HRQoL among RP patients at 6 months and 25 months following treatment, although neither study controlled for baseline HRQoL. Given the immediate nature of RP side effects, and the delayed onset of LDRBT side effects as the prostate receives radiation over a prolonged period, it is likely that small comparative reductions in quality of life occur immediately following RP.

Comparing HRQoL following LDRBT and EBRT also returned mixed results. One study reported significantly higher scores at 6 months for LDRBT compared with EBRT and two studies reported worse scores for LDRBT compared with EBRT at 1 month and 2.5 years following treatment. The two remaining studies showed no difference following EBRT and LDRBT, and were the only two studies to control for baseline HRQoL.

Only one study compared AS with HRQoL and reported no difference in either the physical component or mental component scores of the SF-12 health survey up to 3 years following treatment (Smith et al 2010). However, some AS patients were treated during the follow-up period and this may have an effect on their HRQoL. The assessment of quality of life in men managed with AS could not be adequately considered in this review.

Overall, there is a lack of high-quality evidence to determine whether there are any differences in post-treatment HRQoL between LDRBT, RP and EBRT. While there may be some small differences early after treatment, any differences between treatments appear to be negligible by 6 months.

Summary of the body of evidence for the safety of low-dose-rate brachytherapy

The body of evidence included in this assessment was appraised according to the NHMRC's guidance on clinical practice guideline development (NHMRC 2009). The body of evidence matrix for studies comparing LDRBT with EBRT is presented in Table

24. The evidence-base was poor, containing studies of level III-2 to level IV interventional evidence with moderate to high risk of bias. Despite attempts at matching populations or controlling for potential confounders statistically post hoc, no study satisfactorily removed the effect of patient or clinician treatment selection. Comparing LDRBT with EBRT, there was some inconsistency with results, which is likely to represent genuine uncertainty regarding most safety outcomes. Therefore, given that the differences between LDRBT and EBRT regarding most safety outcomes appear to be minimal, the clinical impact of this assessment is judged to be slight. All studies were performed in developed countries and largely used techniques common in Australia. It is likely that some studies were performed in centres of high patient volume and may report better outcomes than centres of lower patient volume in Australia, although, overall, the generalisability and applicability of the results for LDRBT compared with EBRT are deemed to be good.

Table 24 Assessment of body of evidence for the safety of low-dose-rate brachytherapy compared with external beam radiotherapy for the treatment of localised prostate cancer[a]

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence-base				Level IV studies, or level I to III studies with high risk of bias
Consistency			Some inconsistency reflecting genuine uncertainty around clinical question	
Clinical impact				Slight or restricted
Generalisability		Population(s) studied in body of evidence are similar to the target population		
Applicability		Applicable to Australian healthcare context with few caveats		

[a] For an explanation of this table refer to 'Assessment of the body of evidence' on page 30; Source: NHMRC (2009)

The body of evidence matrix for studies comparing LDRBT with RP is presented in Table 25. The evidence-base was satisfactory, containing a moderate-quality randomised controlled trial (level II evidence) and level III-2 to level IV interventional evidence studies with moderate to high risk of bias. Where baseline characteristics of comparative study arms were not matched, or baseline function was not adjusted for statistically, it was sometimes possible to predict the direction of the confounding on the study outcome; however, baseline function was not always known. Overall, most studies presented consistent results for urinary incontinence, irritative or obstructive symptoms, bowel symptoms and erectile dysfunction. The magnitude of the differences between the arms was not consistent, with some studies showing little or no difference, but the direction of the difference in studies reporting a difference was largely the same. Overall consistency for studies comparing LDRBT with RP was deemed to be good. Given the differences in urinary, bowel and sexual symptoms following the treatments, the clinical impact of this evidence is judged to be substantial. However, a substantial clinical impact does not imply that all patients would clearly select one treatment over another. Rather, the disparate side effect profiles of each treatment will need to be considered by patients and clinicians

when selecting a treatment that will result in the least adverse outcomes for individual patients. Therefore, for a patient with a strong aversion to a particular side effect, the evidence may have a substantial clinical impact. All studies were performed in developed countries with varying levels of screening-detected prostate cancer. In one study the surgical procedure was different to that primarily performed in Australia, and some studies may have taken place in centres with high patient volume. Overall, the generalisability and applicability of studies to the Australian population and the Australian healthcare system is judged to be good.

Table 25 Assessment of body of evidence for the safety of low-dose-rate brachytherapy compared with radical prostatectomy for the treatment of localised prostate cancer[a]

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence-base			Level III studies with low risk of bias, or level I or II studies with moderate risk of bias	
Consistency		Most studies consistent and inconsistency may be explained		
Clinical impact		Substantial		
Generalisability		Population(s) studied in body of evidence are similar to the target population		
Applicability		Applicable to Australian healthcare context with few caveats		

[a] For an explanation of this table refer to 'Assessment of the body of evidence' on page 30; Source: NHMRC (2009)

The body of evidence matrix for studies comparing LDRBT with AS is presented in Table 26. Only one included study identified an AS arm. The study was of a large Australian-based cohort that captured two-thirds of men aged less than 70 years diagnosed with localised prostate cancer over a 2-year period in New South Wales. Baseline characteristics were adjusted for statistically. Ultimately, treatment was selected rather than randomised, and a proportion of men managed with AS received active treatment during the follow-up period. Therefore, the evidence-base is judged to be poor, containing only one level III-2 study with a moderate to high risk of bias. The lack of evidence for the safety of AS, in comparison with LDRBT, must render the observed clinical impact of this evidence as slight. As mentioned, the study was large and based in Australia, collecting data from patients treated in both high- and low-volume centres. Some data from centres with higher than average volumes were not collected; however, overall, the generalisability and applicability of the evidence is excellent.

Table 26 Assessment of body of evidence for the safety of low-dose-rate brachytherapy compared with active surveillance for the treatment of localised prostate cancer[a]

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence base				Level IV studies, or level I to III studies with high risk of bias
Consistency	Not applicable (only one study involving active surveillance was identified)			
Clinical impact				Slight or restricted
Generalisability	Population(s) studied in body of evidence are the same as the target population			
Applicability	Directly applicable to Australian healthcare context			

[a] For an explanation of this table refer to 'Assessment of the body of evidence' on page 30; Source: NHMRC (2009)

Other safety outcomes

There are multiple known immediate side effects of LDRBT, EBRT and RP surgery. These may include blood loss requiring transfusion, infection, venous thrombosis, haematoma, hernia, bowel perforation and patient death. As surgery requires a general anaesthetic, the risks associated with general anaesthesia are also borne by the patient, including allergic reactions, aspiration and death. LDRBT is described as a minimally invasive procedure; however, it still carries the risk of infection and venous thrombosis. It may also carry risks of seed migration through the bloodstream to other organs, usually the lung; or rectourethral fistula, a catastrophic side effect requiring surgery and stool diversion. Loss of individual seeds is not uncommon following LDRBT and they are usually lost into the urethra and then in the urine or ejaculate, although this poses no threat. Migration of the seeds to the lung is less common and has not been linked to short-term adverse consequences (Ankem et al 2002).

Like prostate surgery, LDRBT is usually (although not always) delivered under general anaesthesia. EBRT is a relatively non-invasive procedure and, while it may require the insertion of fiducial markers to assist in the planning and accurate localisation of the prostate, this is customarily done under a local anaesthetic. EBRT may be associated with lethargy, nausea, and skin or mucous membrane reactions that can become infected. One serious side effect associated with all forms of radiation treatment is the development of second malignancies from radiation exposure. As these side effects are largely treatment specific, and perhaps because they are far less common than urinary and bowel side effects and sexual dysfunction, comparative studies rarely report on them in a meaningful way. In most cases such rare side effects are reported as case reports, and have not been captured by this review.

Three large cohort studies using data of men diagnosed with prostate cancer and entered onto the Surveillance, Epidemiology and End Results (SEER) database in the US compared the incidence of radiotherapy-induced second primary cancers (SPCs) among men receiving EBRT, BT and no radiation. Two of the cohort studies involved men who received prostate surgery. All studies used data from the same large US database and involve overlapping populations. These studies have been excluded from this systematic

review on the basis that it is impossible to identify the proportion of the study population that would be eligible. It is likely that a proportion of men had PSA ≥ 10 ng/mL or Gleason score > 7 or had non-localised prostate cancer. In addition, details of treatments are not provided and it is not certain that the treatments delivered resemble those required by this systematic review. In light of this, these results must be interpreted with caution.

In one study comparing radiotherapy treatments with RP (Nieder et al 2008), men who received EBRT or LDRBT were at an increased risk of developing bladder cancer between 5 and 10 years following treatment, compared with RP (RR_{EBRT} = 2.26 [95% CI 1.89, 2.69], RR_{LDRBT} = 1.64 [95% CI 1.03, 2.62]). EBRT patients, but not LDRBT patients, also experienced an increase in rectal cancers relative to men treated with RP (RR_{EBRT} = 1.39 [1.09, 1.79]). Nieder et al (2008) also reported on SPCs occurring earlier than 5 years following treatment and found that men treated with either EBRT or LDRBT had a raised likelihood of developing bladder cancer; however, this result should be considered with caution. Some research indicates that radiation-induced cancers have a latency period of 5–15 years (Jao et al 1987; Thompson et al 1994). It is possible that the increased incidence of bladder cancer among LDRBT and EBRT patients compared with RP patients within the first 5 years suffers from confounding. Men treated with RP appear to be substantially younger than men treated with either EBRT or LDRBT, although the authors have not compared the ages of the cohorts statistically. The authors do, however, adjust for age, race, prostate cancer stage and grade, and year of treatment in a multivariate Cox regression analysis. Compared with men treated with RP, RR_{EBRT} = 1.72 (95% CI 1.55, 1.90) and RR_{LDRBT} = 1.23 (95% CI 1.01, 1.50). However, this statistic still includes bladder cancers that are unlikely to be linked to treatment for prostate cancer. Importantly, when compared with the expected incidence of bladder cancers within the entire SEER database, there was no difference in the incidence of bladder cancer in men treated with LDRBT (RR_{LDRBT} = 1.10 95% CI 0.92, 1.31), while a significant difference remained in men treated with EBRT (RR_{EBRT} = 1.42 95% CI 1.34, 1.50).

In a study comparing the odds of developing SPCs among men receiving radiation with those receiving no radiation (Moon et al 2006), adjusted for age, stage and prostate cancer grade, EBRT patients were at increased odds of developing cancer of the colon, rectum, bladder and non-Hodgkin lymphoma, with odds ratios of 1.26, 1.60, 1.63 and 1.26 ($p<0.05$) respectively. Men receiving LDRBT as a monotherapy had raised odds of acquiring bladder cancer compared with men not receiving radiation, although the difference was not statistically significant. Compared with men who did not receive surgery, men receiving RP had reduced odds (OR_{RP} = 0.78, $p<0.05$) of developing bladder cancer following treatment. Importantly, only cancers that were diagnosed more than 5 years following treatment were included in the analysis, thereby excluding cancers that are unlikely to be linked to treatment for prostate cancer.

In one final study comparing the incidence of SPCs among men treated for prostate cancer with men who received no radiotherapy and no surgery for prostate cancer, patients who received EBRT alone were 1.263 [95% CI 1.167, 1.367] times more likely to acquire an SPC after 5 or more years (Abdel-Wahab et al 2008). SPCs detected earlier than 5 years following treatment were excluded from the analysis. For men treated solely with EBRT, the rate of second malignancies did not appear to change with time. The incidence of SPC increased with time following LDRBT and EBRT combined with LDRBT; and after 9 years following treatment, the mean hazard ratio for both LDRBT and combination EBRT were approximately that of EBRT alone. One potential

confounder in this study is that men receiving EBRT alone tended to be older than LDRBT or combination EBRT patients, and hence other malignancies may be more prevalent in this group. This study reported an additional 162 cancers per 100,000 men that may have been radiation induced, but cautioned that some of the increased cancer incidence may be due to an inherent increased risk of cancer within the population receiving radiotherapy.

All three studies have serious limitations. The SEER database does not contain information on smoking status, which is known to increase the risk of bladder cancer three-fold (Zeegers et al 2002). Also, the studies do not provide treatment details; in particular, they do not report on radiation dosage or the isotope used for interstitial LDRBT (although the isotope used for LDRBT is unlikely to make any difference to the rate of second malignancies).

Is it effective?

Primary effectiveness outcomes

The study by Zhou et al (2009) reported on all-cause survival after radical prostatectomy (RP), low-dose-rate brachytherapy (LDRBT) and external beam radiotherapy (EBRT). Actuarial 7-year survival was higher for LDRBT patients (82%) than EBRT patients (72%), and survival for RP patients was 89%. Comparing the treatment modalities with 'no treatment' as the reference, hazard ratios (Cox regression) for RP, LDRBT and EBRT showed that any treatment was preferable over the option of 'no treatment' ($p<0.0001$). LDRBT was not directly compared statistically with the other treatments; however, the confidence intervals for the hazard ratios for LDRBT and EBRT did not overlap, suggesting a significantly lower likelihood of dying from any cause among LDRBT patients than EBRT patients. Despite correcting for multiple risk factors including Gleason score, comorbidities and age, treatment assignment was not randomised and the effect of confounding cannot be ruled out. Given that the confidence intervals for the hazard ratios for RP and LDRBT did overlap, it is likely that these treatments are not significantly different, even though Kaplan-Meier analysis gave overall survival of 89% for RP and 82% for LDRBT.

Prostate cancer specific survival at 7 years was high among all treatment groups, although RP patients had the best survival (98%), compared with LDRBT (97%) and EBRT (94%). Given the older age of men who are treated for prostate cancer, cancer-specific survival rather than overall survival may be a more accurate representation of treatment effectiveness. Cancer-specific survival for RP and LDRBT is comparable when adjustment is made for clinical stage, Gleason score and other risk factors, while EBRT outcomes are slightly less favourable. Hazard ratios for prostate cancer specific survival indicated that RP and LDRBT were significantly more effective than 'no treatment' ($p<0.0001$ and $p=0.018$ respectively). However, the confidence intervals for all treatments overlapped. Wide confidence intervals in the LDRBT and EBRT groups were apparent—potentially due to small patient numbers—and so accurate comparisons of cancer-specific survival between the treatments cannot be made.

The analysis by Zhou and colleagues (2009) attempted to control for important risk factors, but the large differences observed in overall survival are unlikely to represent real differences in treatment effectiveness. The results for prostate cancer specific survival, which only show small differences between the treatments, indicate that disparities in overall survival are a consequence of unknown or unaccounted-for confounding factors. Furthermore, no information on PSA was obtainable from the databases sourced for this study. The authors admit that pre-treatment PSA > 10 ng/mL is an important risk factor for prostate cancer specific death, and the lack of PSA data makes meaningful conclusions about the effectiveness of the various treatment modalities difficult. International guidelines contraindicate LDRBT for patients with PSA > 10 ng/mL, whereas patients with a broader range of PSA values are treated with RP and EBRT. Therefore, selection of patients with lower PSA values for LDRBT will result in improved outcomes for LDRBT patients compared with RP and EBRT. The extent of any such bias could not be measured.

Cancer stage is correlated with PSA (Partin et al 2001) and, while large disparities between the treatment groups in terms of PSA may be reflected in differences in recorded stage,

only small differences were noted. Therefore, it is unlikely that baseline PSA levels differed dramatically among patient groups.

The database from which Gleason score and stage data were sourced is routinely updated following RP, and evidence from case series suggests that 30–40% of biopsies are assigned a higher grade on review (Capitanio et al 2009). This means that, while a true Gleason score will be known for RP patients, a proportion of LDRBT and EBRT patients assigned a score of Gleason 6 will in fact be Gleason 7, and some of those with a biopsy indicating Gleason 7 will have a true score of Gleason 8. Since it is likely that, in a proportion of patients thought to be low-risk, the biopsy Gleason score will underestimate the true Gleason score, the effectiveness of LDRBT and EBRT may appear reduced in comparison with RP. Although the direction of any such bias is likely to work *against* LDRBT, cancer-specific survival was found to be similar among LDRBT and RP patients.

Another limitation of the study by Zhou et al (2009) was adjustment for comorbidity using the Charlson Index, which provides measures based on hospital admissions and outpatient visits. Other conditions for which patients did not receive medical care (functional dependence, performance status and geriatric conditions) may have been present, uncaptured by the Charlson Index but influencing the findings of this study.

In addition, applicability of this study to the Australian context may have some limitations. It is probable, given the large sample size and the common use of palladium for LDRBT in the US, that a number of patients underwent treatment with palladium. However, one multicentre randomised study has demonstrated that iodine and palladium yield similar results for bNED at 3 years (Wallner et al 2003), and it would not be expected that non-prostate cancer specific survival would differ greatly on the basis of the type of radioactive implants used for LDRBT. Whether comparable secondary measures (bNED) of effectiveness for seeds with different radioactive properties translate to clinically comparable prostate-specific survival in the long term is uncertain on the basis of the evidence available for this review.

There also remains the concern that an unknown proportion of patients did not meet the eligibility criteria for this review. Despite stratified results, which made data for patients with localised disease available for separate analysis, an unknown number of these patients had Gleason scores in the range 8–10. These patients may have influenced the outcomes of the study and would not be eligible for LDRBT according to current criteria in Australia.

Data from the lower quality studies (Pickles et al 2009; Vicini et al 2002) did not refute the conclusions given above.

Despite the potential risk of bias in Zhou et al (2009), the directions of the most important biases in this study are not in favour of LDRBT. However, LDRBT still performed acceptably under such circumstances. Randomised controlled trials capable of addressing known and unknown confounding factors have rarely been undertaken in this area due to strong patient preferences for particular treatment options and selection for side effect profiles. On the basis of the results, it is reasonable to conclude that LDRBT is no worse than RP and EBRT in terms of 7-year overall and disease-specific survival.

Secondary effectiveness outcomes

Biochemical disease-free survival

The randomised controlled trial by Giberti et al (2009) reported 5-year bNED for 174 out of the 200 recruited low-risk prostate cancer patients undergoing RP or LDRBT. In the RP and LDRBT groups, 5-year bNED was 91% and 91.7%, respectively, but no definition of bNED was provided.

The main strength of the study by Giberti et al (2009) was the randomised design that provided patient groups with similar prognostic variables and other baseline characteristics for direct comparison. However, there is no evidence of time-to-event analysis, and statistical methods used to compare biochemical recurrence between men treated with RP and LDRBT may be inappropriate. The authors reported that a chi-squared analysis or Fisher's exact test was used to compare 5-year bNED, and no adjustment for losses to follow-up occurred. The authors did not discuss the characteristics of patients lost to follow-up and no sensitivity analysis was performed; therefore, the relapse status of patients lost to follow-up is unaccounted for, which could influence bNED outcomes in an unknown direction. Importantly, the definitions of biochemical recurrence were not reported and therefore comparisons of bNED between men treated with RP and those treated with LDRBT may be influenced by systematic differences in the sensitivity or specificity of the definitions used for recurrence (Nielsen et al 2008).

Wong and colleagues (2009) reported 5-year bNED for 853 patients undergoing LDRBT or EBRT in two modalities—3D conformal and intensity modulated radiotherapy (IMRT)—and no significant differences were observed between the treatments. As with all studies in the evidence-base, this study was subject to physician and patient preferences for treatments and, consequently, the degree of bias that may have been introduced is uncertain. The distribution of palladium-treated LDRBT patients is unknown and therefore it is difficult to judge whether the majority of low-risk patients did in fact receive treatment with iodine seeds. Given that palladium is not currently available in Australia, the generalisability of these results may be questionable. Across all treatments only small numbers of patients recurred biochemically and, for low-risk patients, LDRBT and either 3D-CRT or IMRT appeared equally effective.

Beyer & Brachman (2000) found no statistically significant differences between patients treated with LDRBT or EBRT for either 5-year or 7-year freedom from biochemical recurrence. Prognostic variables (PSA and Gleason score) were taken into account in the analysis, but the authors indicate that bNED at both 5 and 7 years for low-risk patients (PSA < 10 ng/mL) in both the EBRT and LDRBT groups was lower than observed in other studies with similar patients. The authors postulate that pathological assessment of biopsy specimens may be inconsistent and inaccurately reflect patients' true Gleason scores. They support this hypothesis by reporting that biochemical recurrence in their study did not stratify well by Gleason score and that in wider practice 40–76% of specimens are assigned a different (often higher) score on review. However, under-grading of Gleason scores was likely to be uniform between the treatment groups (EBRT and LDRBT) and therefore unlikely to affect treatment comparisons.

Pickles et al (2010) used a matched-pair design in patients treated with LDRBT and EBRT. Five-year bNED was higher among LDRBT patients (94%) than EBRT patients (88%) for the low-risk group ($p<0.001$). For the intermediate-risk group, bNED was 100% for LDRBT and 78% for EBRT patients ($p\leq0.016$). Overall, bNED was 95.2% for

LDRBT and 84.7% for EBRT patients ($p<0.001$), indicating that only 5% of LDRBT patients relapsed while 15% of EBRT patients experienced biochemical recurrence. However, the PSA doubling time among those who experienced biochemical relapse was a median of 6 months in the LDRBT group and 24 months in the EBRT group ($p<0.001$). The slower PSA doubling time in EBRT patients could well reflect the persistence of local disease caused by under-dosage with EBRT, while faster PSA doubling among the few LDRBT patients who experience relapse is likely to indicate failure resulting from metastatic disease outside the irradiated treatment area. In a review article (Ganswindt et al 2005), low-risk patients benefited from dose escalation up to 70–72 Gy; therefore, less than one-quarter of patients in the analysis by Pickles et al (2010) were likely to have been optimally dosed (the median dosage was 68 Gy and only 25% of EBRT patients received a dosage in excess of 68 Gy).

The main strengths of the study by Pickles and colleagues (2010) were the matched-pair design and the ability to obtain PSA data and to stratify results on the basis of low- and intermediate-risk groups. Patients were matched on all key predictors of bNED, such as Gleason score, PSA level, clinical stage and percentage of positive cores, but not age. Despite age being an important baseline characteristic when considering all-cause survival, it is far less likely to influence secondary measures of disease-specific survival such as bNED. There are, however, some limitations. In particular, it is not clear whether the relatively small number of patients in the matched analysis would be representative of the general Canadian population, or be generalisable to Australia. However, the authors did conduct a secondary analysis of 601 patients deemed eligible but who were not successfully matched. Five-year bNED for the unmatched cohort (95.3% and 81% for LDRBT and EBRT patients respectively) was similar to that observed for the matched cohort (95.2% and 84.7% for LDRBT and EBRT patients respectively), but statistical significance was not reported. Even if a strong statistical difference had been reported, it is highly unlikely that a post-hoc analysis would increase the external validity of the results. On the contrary, such an analysis would reintroduce known confounders, including age, PSA and cancer stage, for which matching was able to adjust.

Studies that considered bNED were all of moderate quality and the majority (Beyer & Brachman 2000; Giberti et al 2009; Wong et al 2009) found no differences between prostate cancer treatments. Some evidence suggested that bNED may be as much as 20% greater among LDRBT patients compared with EBRT patients when considering intermediate-risk patients but, overall, the difference is closer to 10% (Pickles et al 2010). Given that three-quarters of the participants in the EBRT arm received suboptimal dosages, these results need to be interpreted with caution. The other studies that considered bNED found no significant differences between treatments or gave no evidence of a valid statistical comparison (Vicini et al 2002). All studies that assessed bNED are likely to have been biased, but the extent of the bias is unable to be quantified and its direction is unknown.

Summary of the body of evidence for the effectiveness of low-dose-rate brachytherapy

The body of evidence included in this assessment was appraised according to the NHMRC's guidance on clinical practice guideline development (NHMRC 2009). The body of evidence matrix for studies comparing LDRBT with EBRT and RP is presented in Table 27. No studies that included active surveillance (AS) as a comparator were identified and therefore AS was not assessed. In studies that compared LDRBT with

EBRT and RP, the evidence-base was satisfactory, containing one study of level II and four studies of level III interventional evidence with low to moderate risk of bias. For studies that presented primary effectiveness outcomes, the main source of potential bias was routine updating of Gleason scores for RP patients (Zhou et al 2009); however, despite this, LDRBT still performed similarly to RP. The studies that assessed secondary outcomes were subject to biases from physician and patient preferences, and other biases for which the size and direction of influence could not be determined. Most of the studies were consistent in showing that primary and secondary effectiveness outcomes for LDRBT were at least no worse than for RP or EBRT. In one instance (Pickles et al 2010) bNED results appeared more favourable for LDRBT than EBRT, but this was possibly a reflection of suboptimal radiation dosing among EBRT patients. Given that there was uncertainty regarding the extent and direction of bias in the studies that presented secondary effectiveness, and only one moderate-quality study on primary effectiveness reported outcomes for LDRBT, EBRT and RP, the clinical impact of this evidence is limited. All studies were undertaken in developed countries and the majority of patients had localised prostate cancer and were generalisable to the target population within Australia. However, an unknown proportion of LDRBT patients studied by Zhou et al (2009) were likely to have been treated with palladium. Consequently, the results are applicable to the Australian healthcare context only with some reservations.

Table 27 Assessment of body of evidence for the effectiveness of low-dose-rate brachytherapy compared with external beam radiotherapy and radical prostatectomy for the treatment of localised prostate cancer[a,b]

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence-base			Level III studies with low risk of bias, or level I or II studies with moderate risk of bias	
Consistency		Most studies consistent and inconsistency may be explained		
Clinical impact				Slight or restricted
Generalisability		Population(s) studied in body of evidence are similar to the target population		
Applicability		Applicable to Australian healthcare context with few caveats		

[a] For an explanation of this table refer to 'Assessment of the body of evidence' on page 30; Source: NHMRC (2009)

[b] No studies for active surveillance were identified and therefore this comparator was not assessed in the body of evidence matrix.

What are the economic considerations?

Cost and cost-effectiveness

One health technology assessment (HTA) combining the findings of three systematic reviews and three comparative studies assessed the economic considerations of low-dose-rate brachytherapy (LDRBT) as a treatment for localised prostate cancer. No studies of the costs of LDRBT compared with external beam radiotherapy (EBRT), radical prostatectomy (RP) or active surveillance (AS) in an Australian setting were identified.

Two of the comparative studies reported similar costs associated with LDRBT compared with RP and one reported that costs were substantially greater with LDRBT. While all three studies describe RP and LDRBT procedures that are similar to those performed in Australia, the transferability of costs from international studies is unclear.

One HTA combined the safety results from three systematic reviews of LDRBT and proton beam therapy, RP and AS, and IMRT (a form of EBRT). The HTA and systematic reviews were all undertaken by the Institute for Clinical and Economic Review. The report contained a cost–utility analysis of the treatments using a Markov model. The transition probabilities and health state utilities were sourced from the literature, and costs were sourced from published studies, interviews with clinicians and Medicare. The three systematic reviews informed the rates of treatment-related side effects for each of the treatments.

The base case for the model found that, compared with RP, LDRBT resulted in 0.3 more quality adjusted life years (QALYs) at a reduced cost. IMRT also resulted in more QALYs (0.27) although at an incremental cost of US$9,513, resulting in an incremental cost per QALY of US$35,233. AS provided 1.15 more QALYs than RP at an incremental cost of US$2,074 or US$1,803 per QALY.

The model assumes that all treatments are equally effective regarding survival outcomes, and hence any difference in QALYs following treatment will be due to the side effects of each treatment. Importantly, equivalent effectiveness has been reported in this current review. As mentioned, the rates of the side effects were informed by the three systematic reviews undertaken by the Institute for Clinical and Economic Review. Unfortunately, the systematic reviews were of moderate to low quality and relied heavily on low-level intervention evidence (primarily case series).

Given the overall similar cost-effectiveness of all treatments, accepting the substantial uncertainties surrounding the model, it is difficult to conclude the superiority of any one treatment from an economic viewpoint. In particular, the model has costed treatments within the US, which may differ markedly to the costs for the same treatments in Australia.

The generalisability of health economic data from country to country is limited by the degree of similarity between health systems and populations. For the most part, populations and disease characteristics are similar across developed countries; however, variations in wages, methods of healthcare provider reimbursement, physician liability,

available technology and general organisational differences may limit the transferability of cost data from one country to another (Welte et al 2004).

Financial impact analysis

Estimating the likely number of men who would be eligible for ^{125}I LDRBT is difficult given the lack of published national epidemiological data stratifying men by cancer stage or grade. However, using data from two recently published studies, one from South Australia (Beckmann et al 2009) and one from New South Wales (Smith et al 2010), the likely number of men eligible for LDRBT has been estimated at 5,000 in 1 year. This calculation has been addressed in the section on 'Potential utilisation' on page 12. The costs associated with the treatment of men with Gleason 7 prostate cancer are higher, to reflect a greater need for pre-treatment staging scans and the increased likelihood of LHRHa use among men receiving EBRT. Therefore, it is important to estimate the likely proportion of men with Gleason ≤ 6 and Gleason 7 cancer among men with localised prostate cancer. Our best estimate of this ratio is that 55% of men are diagnosed with Gleason ≤ 6 and 45% with Gleason 7 (Shao et al 2009).

All costs are discounted at 5% per year with a half-cycle correction, with the exception of AS costs accrued in the first year.

Scenario 1—BT, EBRT and RP

Overall, the costs associated with LDRBT, EBRT and RP are similar. Assuming that 70% of men treated with LDRBT and 75% with RP are treated in the private healthcare sector, the current annual cost of treating 5,000 men with LDRBT, EBRT and RP (ie excluding AS) is estimated at $66.727 million. LDRBT is marginally more costly than RP, with an incremental cost of LDRBT per patient of $37; and marginally less costly than EBRT, with an incremental cost saving per patient of $105. Obviously, this difference will be sensitive to even small variations in practice regarding work-up, treatment or post-treatment monitoring.

Despite similarities in overall cost, the source of funding for each treatment differs substantially. The MBS is responsible for a greater portion of the cost associated with EBRT, given that it is the only treatment to be delivered entirely on an outpatient basis. LDRBT and RP are performed in a hospital environment and a greater proportion of their overall cost is borne by state/territory governments or by the patient/private insurer. In addition, the largest single expenditure for LDRBT is the cost of the BT seeds, currently listed at approximately $7,000 per patient, while the largest expenditure for RP is the cost of hospitalisation, which is between $8,685 (not including procedural costs) in a private setting and $13,874 (including procedural costs) in a public setting. Both of these expenses are borne by either the patient or his private insurer in a private hospital setting, or by the state/territory governments in a public hospital setting. While the cost to the MBS is greater for EBRT, the substantial saving to the MBS when patients are treated with LDRBT and RP is entirely attributable to the redistribution of costs to other sectors of the Australian healthcare system.

One important omission in this analysis is the increasing use of robot-assisted laparoscopic prostatectomy (RALP). Costs associated with RALP are higher than with

standard open retropubic prostatectomy and were reported as $4,717[13] higher in a 2006 Australian systematic review (Medical Services Advisory Committee 2006). Therefore, compared with LDRBT, treating men with RALP will result in an additional cost of $4,680 per patient, borne either by the patient/private insurer in a private hospital setting, or absorbed by the state/territory government in a public hospital setting.

Scenario 2—BT, EBRT, RP and AS

The likely utilisation of AS in Australia is uncertain. One source using data accrued from October 2000 to October 2002 reported that 20% of men diagnosed with Gleason ≤ 6 prostate cancer initially opted for AS (Smith et al 2010). Among men with Gleason 7 prostate cancer, AS was observed in less than 3.5% in the same study. The appropriateness of AS among men with Gleason 7 prostate cancer is unclear, and it was decided a priori that it would not be considered an appropriate comparator for LDRBT in men diagnosed with Gleason 7 disease. Consequently, the base case has been costed using a 20% uptake of AS among Gleason ≤ 6 disease only, with the remaining men diagnosed with Gleason ≤ 6 and all men with Gleason 7 prostate cancer opting equally for one of the active treatments.

The cost of AS will be sensitive to the proportion of men opting out of AS. For the base case it is assumed that 57% of men will opt out of AS by 10 years at the rate observed in the study by van den Bergh et al 2009.

The overall discounted annual cost to the Australian healthcare system of treating 5,000 men with a combination of LDRBT, EBRT, RP and AS is $65.684 million. This represents a cost saving of approximately $2.583 million over the same scenario without the use of AS. The total cost to the MBS is $28.934 million, with over half the cost being generated by men who initially opt for EBRT. The cost to the patient/private insurer is $25.790 million, primarily as a result of the expenses incurred by LDRBT seeds and RP hospitalisation in a private healthcare setting.

If the uptake of AS among men with Gleason ≤ 6 prostate cancer changes or the retention rate of men while on AS alters, then the total overall costs of treating 5,000 considered to be eligible for LDRBT will also change. Assuming a higher treatment-free survival, with 74% of men remaining on AS at 10 years (Soloway et al 2010), the overall cost to the Australian healthcare system of managing 5,000 men with localised prostate cancer decreases to $64.181 million. If, in addition to an increased retention rate while on AS, 50% of men diagnosed with Gleason ≤ 6 prostate cancer opt for AS, the cost to the Australian healthcare system will decrease to $58.051 million.

Very low rates of retention of men on AS will result in increased costs that would approach those of Scenario 1 (in which AS was not used).

Protocols for following men on AS are varied and thus will have differing cost implications. However, the cost of monitoring a patient on AS would have to increase by four- to five-fold over that proposed in this analysis before the costs associated with AS would equal those associated with immediate active treatment.

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[13] $4,262 more costly in May 2006 (date report published), inflated (using the RBA calculator at http://www.rba.gov.au/calculator/ - accessed 27/10/2010) over 3.5 years at an average inflation rate of 2.9% gives a value of $4,717 in present day Australian dollars.

Most importantly, whether men are able to avoid treatment altogether or merely delay it, the time spent under AS, with proper reassurance, will represent time spent without the potentially lifelong side effects of active treatment. This is supported by the cost–utility analysis by Ollendorf et al (2009) in which the average patient under AS experienced 1.15 more QALYs than men who received immediate RP. This benefit is gained despite Ollendorf's model's moving more than half of all men under AS into active treatment over the duration of the model.

More accurate identification of men who are likely to require active treatment will improve the retention of men on AS. This will allow men to avoid unnecessary treatments and their related side effects, and will reduce the economic costs of treating localised prostate cancer for both patients and the Australian healthcare system.

Other relevant considerations

Expert opinion

In July 2007, following an application to the Department of Health and Ageing from the Australian and New Zealand Association of Urological Surgeons (ANZAUS), the indications for MBS reimbursement of low-dose-rate brachytherapy (LDRBT) were increased to include patients with Gleason 7 prostate cancer. As indicated earlier under 'Intended Purpose' on page 5, the treatment of men with Gleason 7 prostate cancer with LDRBT *alone* appears to be at odds with many international guidelines.

Gleason score is a strong prognostic indicator for oncological and therefore overall survival outcomes (Andren et al 2006), and it is well recognised that men with a Gleason score of 7 but with a primary Gleason grade of 4 fare poorly compared with men who have a primary Gleason grade of 3 (Burdick et al 2009; Chan et al 2000; Kang et al 2007; Khoddami et al 2004; Lau et al 2001; Makarov et al 2002; Rasiah et al 2003; Stark et al 2009). One reason for this may be related to the differences in likelihood that cancer cells have spread beyond the prostate. Partin et al (2001) reported that, among men with Gleason scores of 7, those with a primary grade of 4 were found to have prostate cancer beyond the prostate in 57% of cases.

This systematic review was planned with the aim of stratifying patient outcomes by Gleason score—specifically into a Gleason ≤ 6 group, a Gleason 3+4=7 group and a Gleason 4+3=7 group. Unfortunately, the overwhelming majority of papers included in this review tended either to treat only low-risk patients (Gleason score ≤ 6) or not to separate patients on the basis of Gleason score/grade. A proportion of papers that included patients with a Gleason score of 7 were excluded because the patients had other intermediate- or high-risk characteristics that rendered them ineligible.

The literature reports conflicting effects of primary Gleason grade among men with Gleason score 7 on the outcomes of LDRBT. Potters et al (2003) and Burdick et al (2009) found statistically inferior results among men with Gleason 4+3 compared with Gleason 3+4 scores, whereas Merrick et al (2007) did not show a difference. Munro et al (2010) reported a greater proportion of Gleason 4+3 disease recurring by 8 years following treatment but the trend was not statistically significant. Irrespective of whether Gleason 4+3 disease is the same or worse than Gleason 3+4 disease, it is not clear whether treatment with surgery or EBRT results in better outcomes than LDRBT.

Despite the lack of evidence found by this review, as well as in the additional searched literature, to show a difference in outcomes between men with Gleason 3+4=7 and Gleason 4+3=7 disease, the Advisory Panel has reservations about endorsing the use of LDRBT for treating Gleason 4+3=7 prostate cancer. Given the high expected rate of extracapsular extension among men with Gleason 4+3=7 disease, LDRBT, which has limited extracapsular effect, may be a less suitable treatment option than either EBRT or RP.

Site approval / accreditation

LDRBT, like EBRT, requires a purpose-built radiation treatment facility and a multidisciplinary team of appropriately trained staff. Not unlike RP, the volume of patients treated by an LDRBT team will be an important predictor of implant adequacy and ultimate patient outcomes. Recognising that there is probably a learning curve involved with the delivery of LDRBT (Acher et al 2006; Keyes et al 2006; Lee et al 2000; Liu et al 2010; Tanaka et al 2009), adequate training and a continued minimum patient throughput for an LDRBT team is essential to ensure the best possible outcomes of the procedure. Defining the required standards of training and experience is the role of the relevant professional bodies.

Access and equity

Public versus private sectors

Currently, about 70% of LDRBT procedures occur in the private healthcare sector. Access to LDRBT in public hospitals is limited primarily due to the funding arrangements for the BT seeds. While a number of public hospitals offer LDRBT, the number of procedures they are able to perform is limited by the amount of funding they receive from the state/territory governments. Given the likely small overall differences in the costs of LDRBT, RP and EBRT, decisions to fund one treatment over another likely represent efforts at limiting the cost implications for particular payers. The costs to the state/territory governments will be approximately the same for men treated with LDRBT and RP, but will be higher than treating men with EBRT (for which the MBS bears most of the cost in both the public and private sectors).

The restriction on the number of LDRBT procedures in the public sector will mean that some uninsured men will be unable to access their preferred choice of treatment or will have to pay the full amount for treatment in the private sector.

Greater funding of the LDRBT procedure in the public sector will improve equity. This may be particularly important for uninsured men in non-metropolitan areas who may benefit from the shorter duration of treatment needed for LDRBT. In addition, LDRBT teams in public hospitals will be exposed to a higher volume of procedures, which will improve expertise and the overall quality and efficiency of the service. If greater access to LDRBT in the public sector reduces the number of men opting for EBRT, there may be a cost saving to the MBS that could be used to subsidise the cost of BT seeds in the public sector.

The out-of-pocket expenses for patients undergoing LDRBT in the private sector are currently substantial. If LDRBT becomes more available in the public sector, there is a risk that patients who would have undergone LDRBT in the private sector would opt for

treatment in the public sector. Therefore, judicious subsidy of BT seeds for private patients may ensure that both public and private sectors can continue to offer LDRBT as a treatment option for localised prostate cancer on a more equitable basis.

Rural versus metropolitan

Due to the requirement for a highly specialised team and an expensive purpose-built facility, the provision of a LDRBT service outside of metropolitan areas is unlikely to be clinically optimal or cost effective.

However, given the brevity of the treatment (typically 1–2 days), LDRBT for prostate cancer represents an attractive alternative to EBRT (which is delivered in an outpatient setting over 7–8 weeks) for patients who must travel from rural or remote areas for treatment. In addition, because many of the services required for the preparation of the treatment (staging, TRUS and urinary flow rate) may be available in larger regional centres, the travel necessary for a rural patient may be limited to that required for the procedure alone.

To facilitate access to LDRBT for men living in rural or remote areas, it is important that adequate access to general practitioners is available to ensure that a diagnosis of prostate cancer is made early and while radical treatment remains an option. There is some evidence that Australian men residing in rural areas are less likely to access curative treatments and more likely to die from prostate cancer than their metropolitan counterparts (Coory & Baade 2005; Hall et al 2005). Without access to high-quality primary health care, the diagnosis of prostate cancer may be delayed until it is symptomatic, at which time the disease may be too advanced for LDRBT. Support through training and connections with specialist centres as well as incentives for general practitioners may ensure early and adequate management of prostate cancer in men from rural and regional areas. It is also important to provide access to an initial consultation with a cancer specialist, either a urologist or radiation oncologist, who can assess the patient and inform him of suitable treatment options for localised prostate cancer, including LDRBT.

As LDRBT may require only a very brief stay in a metropolitan area, there may be a substantial cost saving in subsidised travel and accommodation in comparison with treatments of longer duration, such as EBRT, for men travelling from rural or remote areas. Currently, all states and territories have patient accommodation and travel schemes (information available at: http://www.health.gov.au/internet/main/publishing.nsf/Content/health-roi-radiother-index.htm#Accomodation)

LDRBT requires a follow-up scan at approximately 1 month to assess the adequacy of the prostate implant. This process requires access to a CT scanner, after which the image is assessed by a LDRBT expert who can reconstruct the distribution of dose throughout the prostate by mapping the implanted seeds. Ideally, regional centres that can provide a CT scan of the relevant region could be used, with the CT images sent electronically or copied to a storage device, such as a compact disc, and posted to the LDRBT centre for post-implant dosimetric verification. Investment in technology and data linkage to enable services like these to exist will be important for reducing the added burden of seeking treatment for men in rural or remote areas.

Along with disease monitoring and the treatment of patient side effects, follow-up schedules should be sensitive to the travel implications for rural or remote patients.

Where possible, patients should be offered follow-up with specialists who visit regional areas, or with general practitioners who are adequately trained and provided with guidelines for ongoing prostate cancer monitoring.

For longer term follow-up, research into the effectiveness of internet or telecommunication-based consultations would lessen the burden of travel for rural and remote patients.

In conclusion, while developing radiation oncology services in areas with smaller populations may not be logistically feasible, the following approaches will minimise the disadvantages for men from rural or remote areas seeking treatment for prostate cancer:

- developing strong links between smaller centres that service rural and remote areas and the radiation oncology services of metropolitan areas

- ensuring adequate prostate cancer specific training of and incentives for general practitioners in rural and remote areas to facilitate the timely diagnosis of prostate cancer and the monitoring of patients following prostate cancer treatment

- investment in technology that will improve the efficiency of managing patients, such as linking CT scanners in regional areas with specialist centres and internet or telecommunication for patient consultations when appropriate.

A trial offering radiotherapy in regional centres of Victoria was jointly run by the Australian and Victorian governments between 2002 and 2007 (Australian Government Department of Health and Ageing 2009a). The trial involved the operation of single radiotherapy machines in regional Victoria to service the surrounding population. These single machine units were operated as a spoke of larger central specialist radiation oncology hubs. It was found that the cost of providing radiation oncology treatments in Ballarat was similar to that in East Melbourne. However, the total cost to the patient or carer represented an overall saving of at least $400,000. This approach requires careful planning and, while not an option for all regional centres, it should be a consideration for policy makers.

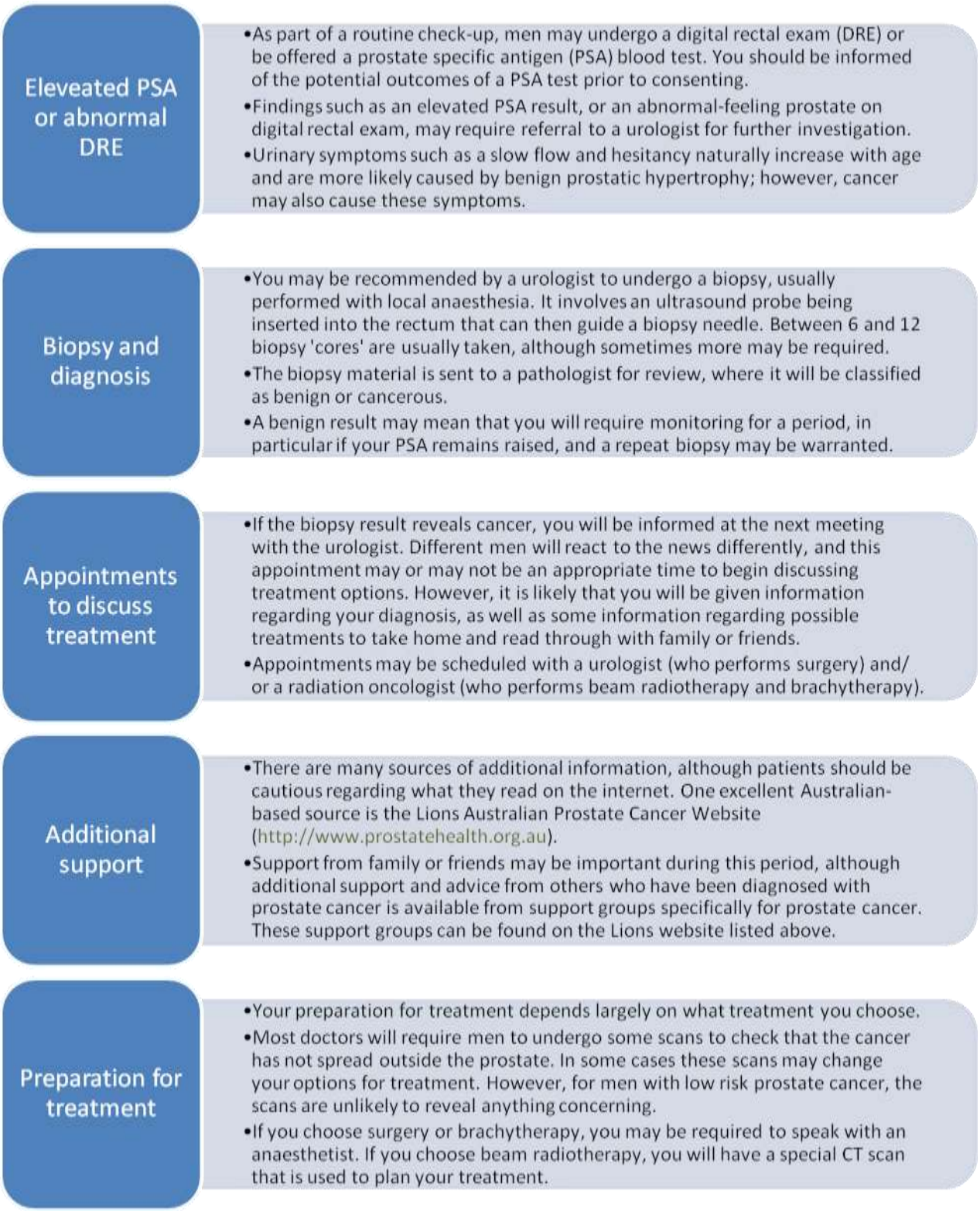
Patient journey

A diagnosis of cancer can be a frightening and uncertain period in a person's life. Different men will respond to the diagnosis of prostate cancer differently and each experience will be unique. However, most patients who are diagnosed with localised (confined to the prostate) low- to moderate-risk prostate cancer will choose one of four paths—surgery, EBRT, LDRBT or AS (close monitoring with the intention to intervene if the cancer shows signs of progressing).

While most men with low- to moderate-risk prostate cancer may be suitable for all four management options, some patient characteristics may preclude some men from some options. For example, other medical conditions may increase the risks associated with surgery, or a very large prostate will make LDRBT difficult to perform. In addition, changes in PSA level or concerning findings on biopsy may make AS a less safe option.

Figure 7 presents a typical journey for a man who is diagnosed with localised prostate cancer.

Figure 7 Patient journey for a man diagnosed with localised prostate cancer



Surgery

- If you select surgery, you will be admitted the night before or the morning of your procedure. The procedure will take about 2–4 hours and you will probably have to stay in hospital for at least the next day, and probably a little longer.
- Immediately following treatment you will be required to have a catheter for about a week or 10 days, after which it will be removed.
- Common short-term side effects of surgery are pain around the surgical site and leaking urine, for which pads may have to be worn until control is regained.

External beam radiotherapy

- If you select external beam radiotherapy, you will be required to attend a clinic for 15 minutes 5 (or sometimes 4) days a week for about 7 or 8 weeks. You will be placed on a specialised bed (similar to that in a CT scanner) and a machine will deliver a small radiation dose, often from four or more directions.
- Once a week you will meet briefly with a radiation oncologist who will assess your progress and manage any side effects you may have.
- Common short-term side effects of beam radiotherapy are changes in bowel habits, increased urinary frequency and occasionally pain during urination, for which medication can be prescribed.

Brachytherapy

- If you select brachytherapy, you may be admitted for a short stay (about 1 day) or the procedure may be performed in a single day. During the procedure (under general anaesthetic) multiple biopsy-like needles are placed through the skin and into your prostate.
- Small radioactive seeds are left in your prostate that will emit radiation over an extended period. The radiation poses no risk to others. Sometimes you will pass a seed, either in your urine or ejaculate; therefore, you will be asked to strain your urine for 2 weeks and wear a condom during intercourse.
- Common short-term side effects of brachytherapy are difficulty urinating (which may require short-term catheterisation) and pain around the needle insertion sites on your perineum.

Active surveillance

- If you select active surveillance, you will be strictly monitored by your urologist or your GP. You may be required to undergo a second biopsy to ensure that active surveillance is an appropriate choice for you.
- You will be required to have frequent PSA tests and a digital rectal exam at least once every year.
- Repeat biopsies may be warranted after a certain time, or if there are changes to your PSA or the feel of your prostate.
- Rigorous monitoring will continue for at least 5 years or longer, and you will probably be followed for the rest of your life.
- At any time your urologist or GP may identify a concerning change to your PSA that may warrant active treatment.

Follow-up after treatment

- Follow-up after the treatment may be with either or both a urologist and radiation oncologist. This is to make sure everything is going well.
- A PSA test will be done, but not for at least a month following treatment, to gauge the success of the treatment. For surgery, your PSA typically falls quickly to a very low or undetectable level. For beam radiotherapy or brachytherapy, the PSA will fall more slowly over a longer period (a year or longer) and will occasionally rise again (bounce) before it settles.

Further monitoring

- If you are travelling well, your urologist or radiation oncologist may 'discharge' you and you will then be monitored by your GP. This will involve regular PSA tests, about 6 months apart, for some years following the treatment or even for the rest of your life.

Future research

The current systematic review is the third MSAC assessment of ^{125}I LDRBT for localised prostate cancer. Like many technologies, LDRBT has become an established treatment despite a lack of evidence. Furthermore, there is little evidence to support the efficacy of comparators within this review; therefore, a conclusion that LDRBT is as effective as either RP or EBRT does not imply that LDRBT is a more effective treatment than no treatment.

One randomised controlled trial comparing RP with watchful waiting showed an increased overall and cancer-specific survival among men treated with RP (Bill-Axelson et al 2008). The Scandinavian Prostate Cancer Group 4 (SPCG-4) trial showed a difference in cancer-specific survival at 12 years of 5.4% [95% CI 0.2 to 11.1%]. This means that nearly 19 men would have to be treated with RP to prevent one prostate cancer death at 12 years following treatment. Importantly, the effect of treatment on survival did not extend to men diagnosed with prostate cancer over the age of 65 years and, given that this population was largely unscreened, this may represent an even younger cut-off in screened populations.

While it is almost certain that RP is effective in some patients, further clinical research of all modalities of prostate cancer treatment could help to better inform both clinicians and patients of the relative risks and benefits of each treatment choice. RP, EBRT and LDRBT all carry risks of short- and long-term side effects, some of which will adversely affect patient quality of life. Therefore, avoiding overtreatment of men who are not destined to die of prostate cancer or experience prostate cancer related morbidity would represent both an avoidance of treatment-related side effects for the patient and a substantial cost saving to the healthcare system.

Trials (START[14], PRIAS[15], and ProtecT[16]) comparing AS with active treatments are currently underway and may help to assess the risks and benefits of AS as a management option for prostate cancer.

Conclusions

Safety

The assessment of safety-related outcomes following low-dose-rate brachytherapy (LDRBT) for localised prostate cancer involved one randomised controlled trial comparing LDRBT with radical prostatectomy (RP) and 17 studies comparing LDRBT with one or more of: external beam radiotherapy (EBRT), RP and active surveillance (AS). The body of evidence for the safety of LDRBT differed between comparators and has been presented in Table 24, Table 25 and Table 26 in the discussion of this report. While most studies were judged to be of moderate quality, the overall evidence-base was deemed satisfactory for comparisons with RP and poor for comparisons with EBRT and AS. Consistency in studies comparing LDRBT with RP was generally good, although comparisons with EBRT had some inconsistency. Only one study involved comparisons with AS and therefore consistency is not applicable. Many of the differences between LDRBT and RP were large and the clinical impact of the evidence was judged to be substantial; however, as the differences between LDRBT and EBRT were smaller and, in some cases, uncertain, the clinical impact of the evidence was deemed to be slight. Only poor-quality evidence was available for comparisons with AS and treatment effect differences are difficult to ascertain; therefore, the clinical impact was judged to be slight. The evidence for all comparators was found to be generalisable and applicable to the Australian population and healthcare setting.

Meaningful synthesis of results is marred by the large number of tools and methods used to describe similar outcomes. For example, this review has reported on six different questionnaires or clinician-reported scales, none of which are directly comparable. Furthermore, questionnaire-related results are invariably reported as a mean, or a mean change from baseline, across a group. Irrespective of whether there is a significant difference between groups or not, it is impossible to determine what proportion of subjects experienced a clinically meaningful event or change in quality of life (QoL). Consequently, it may be possible to determine whether one treatment performs better or worse than another but an effect size will be difficult to interpret if QoL within groups is not normally distributed. In other words, if most patients experience minimal or clinically insignificant changes, but a small proportion experience devastating changes, the overall mean difference may be small and unrepresentative of the true clinical picture. This is not likely to be an obscure or hypothetical situation. Common sense tells us that there will be large differences in QoL following treatment in men who report serious radiation proctitis or, more commonly, incontinence, compared with those who do not. The mean QoL change for the whole group may be only small but, for the man who is in pain or who is largely incontinent or requires invasive surgery, the change in QoL will be very important.

Patients who receive either LDRBT or EBRT are likely to experience transient irritative or obstructive symptoms. These may manifest as painful urination, increased daytime or nocturnal frequency, haematuria or urge incontinence. For most men these symptoms will abate within 6 months or 1 year following treatment; however, for some men symptoms may persist longer. Irritative or obstructive symptoms are rare following RP and were not assessed for AS.

Urinary incontinence is common soon after RP and far less likely following either LDRBT or EBRT. Most men regain continence following RP by 1 year; however, rates of incontinence continue to be higher at 3 years following RP than either LDRBT or EBRT. It is likely that LDRBT and EBRT may be associated with increased rates of incontinence from baseline, although this may be a consequence of urgency due to bladder or urethral irritation rather than lack of control. Incontinence appears uncommon in men managed with AS.

Urinary function and bother, as measured by QoL instruments, slightly favoured radiation treatments over RP, although the magnitude of the difference is uncertain and probably small.

Patients who are treated with RP experience fewer bowel-related side effects, such as frequency or changes to bowel habit, painful bowel movements, bleeding and incontinence, than men who are treated with LDRBT. Men who are treated with LDRBT may have fewer bowel-related side effects than men who are treated with EBRT. Differences in bowel function and bother across treatments are likely to be large soon after treatment and reduce over time. However, there may still be function- or bother-related detriments at 3 years following treatment among men who receive EBRT. Bowel bother appears uncommon in men managed with AS.

Erectile dysfunction in the community is common among men aged 60 years and older, and increases with age. Differences in age and pre-treatment function of men opting for treatments of localised prostate cancer, as well as the perceived effectiveness of treatment regarding the preservation of erectile function, will seriously confound studies reporting on erectile dysfunction following treatment. The use of medications or aids for erectile dysfunction will also confound treatment effects if their use is disparate across groups.

Erectile dysfunction is far more common following RP than LDRBT, although there may be little difference between LDRBT and EBRT. Differences in reported potency rates across studies may reflect patient selection, treatment technique, surgeon experience or access to rehabilitative treatments following treatment. Erectile dysfunction among men managed with AS could not be assessed.

Overall health-related QoL may be transiently lower in patients following RP compared with LDRBT and EBRT, perhaps reflecting transient high incontinence rates, although this difference is small and does not endure beyond approximately 6 months. Given the large number of treatment side effects that may contribute to reduced QoL in patients following treatment for localised prostate cancer, overall health-related QoL may not be an informative metric for either patients or clinicians. Because patients will have different aversions to different treatment side effects, QoL will be maximised when an informed patient considers the risks associated with each treatment and selects the treatment best suited to himself.

Effectiveness

Primary effectiveness

The available evidence for the primary effectiveness of LDRBT for the treatment of low-risk prostate cancer was of moderate quality overall. Results indicate that LDRBT

effectiveness outcomes at less than 10 years are no different compared with RP and EBRT. The highest quality cohort study reporting on all-cause survival (Zhou et al 2009) found no difference between RP and LDRBT, while results for LDRBT and EBRT were similar. Regardless of the potential for bias, the direction of the most important biases in this study did not favour LDRBT, despite which its performance was still at least comparable to other modalities. Indeed, the weight of evidence presented by Zhou and colleagues (2009) provides reasonable certainty that LDRBT is no worse that RP or EBRT. Randomised controlled trials are lacking (only one included study) due to patient preferences and physician selection on the basis of side effect profiles, and Zhou et al (2009) comprises the best available evidence. Evidence provided by the lower quality studies (Pickles et al 2010; Vicini et al 2002) did not refute these results. The majority of patients examined in these studies had localised prostate cancer and were generalisable to the target population within Australia. However, an unknown proportion of LDRBT patients studied by Zhou et al (2009) were likely to have been treated with palladium. Consequently, the results are applicable to the Australian healthcare context only with some reservations.

Secondary effectiveness

Studies that presented secondary effectiveness were all of moderate quality and the majority (Beyer & Brachman 2000; Giberti et al 2009; Wong et al 2009) found no differences in bNED for LDRBT, EBRT or RP. The randomised controlled trial by Giberti et al (2009) presented 5-year bNED for low-risk prostate cancer patients undergoing RP or LDRBT and found no difference between the two treatments. There were some limitations in the statistical analysis and loss to follow-up was also a problem; however, the direction and size of these potential effects on outcome cannot be known. Giberti et al (2009) was the only level II study to address (secondary) effectiveness outcomes and it is reasonable to conclude, on the basis of the results, that LDRBT for the treatment of low-risk prostate cancer is probably no worse that EBRT in terms of bNED at 5 years. Some evidence (Pickles et al 2010) suggested bNED may be 10% better among LDRBT patients than EBRT patients but, given that three-quarters of the participants in the EBRT arm received suboptimal dosage, these results need to be interpreted with caution. The poor-quality study (Vicini et al 2002) gave no evidence of a valid statistical comparison. Biochemical disease-free survival outcomes for all studies of secondary effectiveness are likely to have been biased, but the extent of the bias is unable to be quantified and its direction is unknown. As a consequence, the results are uncertain.

Economic considerations

The comparative effectiveness of LDRBT, RP, EBRT and AS for the treatment of localised prostate cancer is not known and therefore a cost-effectiveness analysis could not be performed.

Cost–utility analysis

Using the assumption of equal effectiveness regarding survival across treatments, a cost–utility analysis from the US found that men treated with LDRBT for prostate cancer retained more quality adjusted life years (QALYs) than men who received EBRT or RP.

Men initially treated with AS experienced the largest number of QALYs. Costs were from US sources and their generalisability to the Australian healthcare system is uncertain.

Financial impact analysis

The expected number of men who would be eligible for LDRBT is approximately 5,000 per year. The anticipated uptake of LDRBT is approximately 1,400 procedures in 2010, although this is likely to increase.

For the financial impact analysis of LDRBT, two scenarios were costed. The first scenario includes only the cost of active treatments (LDRBT, EBRT and RP) and follow-up over a period of 10 years. The second scenario includes, in addition, the likely uptake of AS among men diagnosed with Gleason ≤ 6 prostate cancer. This scenario reflects the best estimate for the costs associated with the treatment of localised, low- to intermediate-risk prostate cancer in Australia.

Scenario 1

The cost to the MBS of treating one-third of all potentially eligible men with LDRBT is approximately $5.829 million per year. The overall annual cost to the MBS of treating all 5,000 men is estimated at $28.362 million. The cost of LDRBT to the MBS is approximately $1.898 million greater than for RP, and $12.774 million less than for EBRT. Therefore, the estimated financial impact of continued listing on the MBS for LDRBT will depend on how many men select LDRBT instead of RP and LDRBT instead of EBRT. However, LDRBT would have to draw almost seven times as many men from RP than from EBRT to result in an increased net cost to the MBS.

The total cost to the Australian healthcare system for treating 5,000 men with LDRBT, EBRT or RP is approximately $66.726 million per year. The per patient incremental costs of LDRBT compared with EBRT and RP are small, and therefore the financial impact on the Australian healthcare system of continued listing on the MBS for LDRBT will be almost negligible.

Scenario 2

The utilisation of AS in Australia is unknown and a figure of 20% of men with Gleason ≤ 6 disease has been used for costing purposes. Assuming that 57% of men on AS will eventually opt for active treatment, the discounted annual cost to the MBS of treating men with LDRBT is approximately $5.590 million. The overall cost to the MBS of treating men with LDRBT, EBRT, RP or AS is $28.934 million, a small increase from the overall cost to the MBS of just treating men with LDRBT, EBRT or RP. However, the overall annual cost to the Australian healthcare system of treating all 5,000 men with LDRBT, EBRT, RP or AS is approximately $1.043 million less than in scenario 1 (without AS).

The cost of managing men with AS will depend upon the number of men who opt for AS, the cost of the surveillance protocol, the number of men who eventually opt for active treatment, and the treatment that they select. Greater use of AS and a lower transition rate to treatment will ultimately result in a lower cost to the Australian healthcare system.

All treatments for prostate cancer may be accompanied by side effects; therefore, avoiding or delaying treatment among men who do not immediately require it, as is accomplished by AS, may have substantial benefits for quality of life.

Appendix A MSAC terms of reference and membership

The Medical Services Advisory Committee (MSAC) is an independent scientific committee comprising individuals with expertise in clinical medicine, health economics and consumer matters. It advises the Minister for Health and Ageing on whether a new medical service should be publicly funded based on an assessment of its comparative safety, effectiveness, cost-effectiveness and total cost, using the best available evidence. In providing this advice, MSAC may also take other relevant factors into account. This process ensures that Australians have access to medical services that have been shown to be safe and clinically effective, as well as representing value for money for the Australian healthcare system.

MSAC is to:

- advise the Minister for Health and Ageing on medical services that involve new or emerging technologies and procedures, in relation to:
    - the strength of evidence in relation to the comparative safety, effectiveness, cost-effectiveness and total cost of the medical service;
    - whether public funding should be supported for the medical service and, if so, the circumstances under which public funding should be supported;
    - the proposed Medicare Benefits Schedule (MBS) item descriptor and fee for the service where funding through the MBS is supported;
    - the circumstances, where there is uncertainty in relation to the clinical or cost-effectiveness of a service, under which interim public funding of a service should be supported for a specified period, during which defined data collections under agreed clinical protocols would be collected to inform a re-assessment of the service by MSAC at the conclusion of that period;
    - other matters related to the public funding of health services referred by the Minister.
- advise the Australian Health Minister's Advisory Council (AHMAC) on health technology assessments referred under AHMAC arrangements.

MSAC may also establish subcommittees to assist it to effectively undertake its role. MSAC may delegate some of its functions to such subcommittees.

The membership of MSAC at the December 2010 meeting comprised a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	Expertise or affiliation
Professor Robyn Ward (Chair)	Medical Oncology
Associate Professor Frederick Khafagi (Deputy Chair)	Nuclear Medicine
Professor Jim Butler (Chair, Evaluation Sub-committee)	Health Economics
Associate Professor John Atherton	Cardiology
Professor Justin Beilby	General Practice/Research
Associate Professor Michael Bilous	Anatomical Pathology
Professor Jim Bishop AO	Chief Medical Officer (ex-officio member)
Professor Peter Cameron	Trauma and Emergency Medicine
Associate Professor Kirsty Douglas	General Practice/Research
Professor Kwun Fong	Thoracic Medicine
Professor Richard Fox	Medical Oncology
Professor John Horvath	Renal Medicine/Health Workforce
Ms Elizabeth Koff	Health Administration
Professor Helen Lapsley	Health Economics
Professor Peter McCluskey	Ophthalmology
Mr Russell McGowan	Consumer Health Representative
Dr Allan McKenzie	Radiology
Dr Graeme Suthers	Genetics/Pathology
Mr David Swan	AHMAC Representative (ex-officio member)
Professor Ken Thomson	Radiology
Dr Christine Tippett	Obstetrics/Gynaecology
Associate Professor David Winlaw	Paediatric Cardiothoracic Surgery
Dr Caroline Wright	Colorectal Cancer

Appendix B Advisory Panel and Evaluators

Advisory Panel – Application 1089.1 – Brachytherapy for the treatment of prostate cancer

Member	Nomination / Expertise or Affiliation
Associate Professor Fred Khafagi (Chair)	Member of MSAC Nuclear Medicine Physician
Dr Allan McKenzie (Deputy Chair)	Member of MSAC Radiologist
Dr Ross Cartmill	Urologist
Professor Tony Costello	Urologist Prostate Specialist
Professor Gillian Duchesne	Radiation Oncologist Uro-Oncology
Mr Bill McHugh	Expert Consumer
Professor Anatoly Rozenfeld	Medical Radiation Physicist

Evaluation Sub-committee input

Name	Organisation
Professor Andrew Wilson	ESC member

Evaluators

Name	Organisation
Mr David Tamblyn	Adelaide Health Technology Assessment
Mr Ben Ellery	Adelaide Health Technology Assessment
Ms Tracy Merlin	Manager, Adelaide Health Technology Assessment

Appendix C Search strategies

Table 28 Additional sources of literature

Source	Location
Internet	
Australian Clinical Trials Registry	http://www.actr.org.au
NHMRC- National Health and Medical Research Council (Australia)	http://www.health.gov.au/nhmrc/
US Department of Health and Human Services (reports and publications)	http://www.os.dhhs.gov/
New York Academy of Medicine Grey Literature Report	http://www.nyam.org/library/greylit/index.shtml
Trip database	http://www.tripdatabase.com
Current Controlled Trials metaRegister	http://controlled-trials.com/
National Library of Medicine Health Services/Technology Assessment Text	http://text.nlm.nih.gov/
U.K. National Research Register	http://www.update-software.com/National/
Google Scholar	http://scholar.google.com/
Hand searching (journals from 2009)	
Acta Radiologica	Library or electronic access
BJU International	Library or electronic access
Brachytherapy	Library or electronic access
Cancer	Library or electronic access
Cancer Radiothérapie	Library or electronic access
European Urology	Library or electronic access
International Journal of Radiation Oncology, Biology and Physics	Library or electronic access
International Journal of Urology	Library or electronic access
Journal of Clinical Oncology	Library or electronic access
Journal of Urology	Library or electronic access
Radiotherapy and Oncology	Library or electronic access
Seminars in Radiation Oncology	Library or electronic access
Urology	Library or electronic access
Expert clinicians	
Studies other than those found in regular searches	MSAC Advisory Panel
Pearling	
All included articles will have their reference lists searched for additional relevant source material	

Table 29 Consumer and professional websites for additional information

Consumer websites	
Andrology Australia	http://www.andrologyaustralia.org/
Lions Australia Prostate Cancer Website	http://www.prostatehealth.org.au/
Prostate Cancer Foundation of Australia	http://www.prostate.org.au/
Professional societies	
American Urological Association	http://www.auanet.org/
Urological Society of Australia and New Zealand	http://www.urosoc.org.au/
Royal Australian and New Zealand College of Radiologists	http://www.ranzcr.edu.au/
Trans-Tasman Radiation Oncology Group	http://www.trog.com.au/
Medical Oncology Group of Australia	http://www.moga.org.au/
American Brachytherapy Society	http://www.americanbrachytherapy.org/
American Society for Radiation Oncology	http://www.astro.org/
Radiation Therapy Oncology Group	http://www.rtog.org/
European Association of Urological	http://www.uroweb.org/
European Society for Therapeutic Radiology and Oncology	http://www.estro.org/
European Org. for Research and Treatment of Cancer	http://www.eortc.be/
National Cancer Institute	http://www.cancer.gov/
National Cancer Institute of Canada Clinical Trials Group	http://www.ctg.queensu.ca/
Southwest Oncology Group	http://www.swog.org/
Eastern Cooperative Oncology Group	http://www.ecog.org/
Northern Central Cancer Treatment Group	http://ncctg.mayo.edu/

Table 30 Websites of health technology assessment agencies

AUSTRALIA	
Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S)	http://www.surgeons.org/Content/NavigationMenu/Research/ASERNIPS/default.htm
Centre for Clinical Effectiveness, Monash University	http://www.mihsr.monash.org/cce/
Centre for Health Economics, Monash University	http://www.buseco.monash.edu.au/centres/che/
AUSTRIA	
Institute of Technology Assessment / HTA unit	http://www.oeaw.ac.at/ita
CANADA	
Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS)	http://www.aetmis.gouv.qc.ca/site/home.phtml
Alberta Institute of Health Economics (IHE)	http://www.ihe.ca/
The Canadian Agency for Drugs And Technologies in Health (CADTH)	http://www.cadth.ca/index.php/en/
Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database	http://www.chera.ca
Centre for Health Economics and Policy Analysis (CHEPA), McMaster University	http://www.chepa.org
Centre for Health Services and Policy Research (CHSPR), University of British Columbia	http://www.chspr.ubc.ca
Health Utilities Index (HUI)	http://www.fhs.mcmaster.ca/hug/index.htm
Institute for Clinical and Evaluative Studies (ICES)	http://www.ices.on.ca
Saskatchewan Health Quality Council (Canada)	http://www.hqc.sk.ca
DENMARK	
Danish Centre for Evaluation and Health Technology Assessment (DACEHTA)	http://www.sst.dk/english/dacehta.aspx?sc_lang=en
Danish Institute for Health Services Research (DSI)	http://www.dsi.dk/frz_about.htm
FINLAND	
Finnish Office for Health Technology Assessment (FINOHTA)	http://finohta.stakes.fi/EN/index.htm
FRANCE	
L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES)	http://www.anaes.fr/
GERMANY	
German Institute for Medical Documentation and Information (DIMDI) / HTA	http://www.dimdi.de/static/en/index.html
Institute for Quality and Efficiency in Health Care (IQWiG)	http://www.iqwig.de
THE NETHERLANDS	
Health Council of the Netherlands Gezondheidsraad	http://www.gezondheidsraad.nl/en/
Institute for Medical Technology Assessment (Netherlands)	http://www.imta.nl/
NEW ZEALAND	
New Zealand Health Technology Assessment (NZHTA)	http://nzhta.chmeds.ac.nz/
NORWAY	
Norwegian Knowledge Centre for the Health Services	http://www.kunnskapssenteret.no
SPAIN	
Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"l/Health Technology Assessment Agency (AETS)	http://www.isciii.es/
Andalusian Agency for Health Technology Assessment (Spain)	http://www.juntadeandalucia.es/
Catalan Agency for Health Technology Assessment (CAHTA)	http://www.gencat.cat

SWEDEN	
Center for Medical Technology Assessment	http://www.cmt.liu.se/?l=en&sc=true
Swedish Council on Technology Assessment in Health Care (SBU)	http://www.sbu.se/en/
SWITZERLAND	
Swiss Network on Health Technology Assessment (SNHTA)	http://www.snhta.ch/
UNITED KINGDOM	
National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA)	http://www.hta.ac.uk/
NHS Quality Improvement Scotland	http://www.nhshealthquality.org/
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/
The European Information Network on New and Changing Health Technologies	http://www.euroscan.bham.ac.uk/
University of York NHS Centre for Reviews and Dissemination (NHS CRD)	http://www.york.ac.uk/inst/crd/
UNITED STATES	
Agency for Healthcare Research and Quality (AHRQ)	www.effectivehealthcare.ahrq.gov/
Harvard School of Public Health	http://www.hsph.harvard.edu/
Institute for Clinical and Economic Review (ICER)	http://www.icer-review.org/
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org
Minnesota Department of Health (US)	http://www.health.state.mn.us/htac/index.htm
National Information Centre of Health Services Research and Health Care Technology (US)	http://www.nlm.nih.gov/hsrph.html
Oregon Health Resources Commission (US)	http://egov.oregon.gov/DAS/OHPPR/HRC/about_us.shtml
Office of Technology Assessment Archive	http://fas.org/ota
U.S. Blue Cross/ Blue Shield Association Technology Evaluation Center (Tec)	http://www.bcbs.com/blueresources/tec/
Veteran's Affairs Research and Development Technology Assessment Program (US)	http://www.research.va.gov/default.cfm

Appendix D Data tables for urinary side effects

Table 31 Urinary side effects resulting from low-dose-rate brachytherapy, radical prostatectomy, external beam radiotherapy and active surveillance for the treatment of localised prostate cancer

Study	Study design and quality appraisal	Population	Urinary function
(Giberti et al 2009) Single centre, Italy Accrual: May 1999 – October 2002	Randomised controlled trial Level II interventional evidence Downs and Black quality score: **19/27** Overall quality assessment: **Moderate**	**N:** 100 RP patients and 100 LDRBT patients Questionnaires were completed for 89 RP patients and 85 LDRBT patients Exclusion criteria were in accordance with American Brachytherapy Society RP / LDRBT No. patients: 100 / 100 Age, years: 65.2 (57–74) / 65.6 (56–74) Gleason score: 5.9 / 5.7 PSA, ng/mL: 7.8 (3.5–10.0) / 7.5 (2.9–9.3) Values are mean (range) unless otherwise indicated	**Mean scores (p-value) from questionnaires at four time points** (higher scores indicate worse function/symptoms) Pre-treatment / 6 months / 1 year / 5 years IPSS: RP 4.6 / 4.9 (NS)* / 4.7 (NS) / 4.7 (NS) LDRBT 4.9 / 15.2 (<0.01) / 10.1 (0.01) / 5.1 (NS) EORTC-QLQ-PR25: Urinary symptoms RP 9.0 / 17.0 (<0.01) / 10.0 (NS) / 10.0 (NS) LDRBT 8.0 / 36.0 (<0.01) / 15.0 (<0.01) / 17.0 (NS) * p-values for change from pre-treatment value Loss to follow-up is not reported. **Percentage of patients reporting urinary symptoms** 6 months / 1 year / Overall Mild urinary incontinence: RP 13.0 / NR / NR LDRBT NR / NR / NR Severe urinary incontinence: RP 5.4 / NR / NR LDRBT NR / NR / NR Urethral stricture: RP NR / NR / 6.5

Study	Study design and quality appraisal	Population	Urinary function
			LDRBT NR NR 2.0 Irritation: RP NR NR 5.0 LDRBT 80.0 20.0 NR Urinary retention: RP NR NR 10.0 LDRBT NR NR NR
(Eade et al 2008) Single centre, US BT patients: May 1998 – August 2004 EBRT patients: August 2001 – June 2004	Prospective cohort Level III-2 interventional evidence Downs and Black quality score: **19/27** Overall quality assessment**: Moderate**	**N: 374** low-risk prostate cancer patients (as defined by American Joint Committee on Cancer) with Gleason score < 7 EBRT LDRBT n 216 158 Age, years 67.6 (27–81)* 64.7 (42–78) PSA, ng/mL 5.2 (0.4–9.6) 5.2 (0.5–9.8) * Values are median (range). No patients were lost to follow-up.	**Urinary outcomes, RTOG scale** EBRT (n=216) LDRBT (n=158) p-value Acute side effects: GU* ≥ grade 2 15.0 (6.9) 42.0 (26.6) <0.001 GU grade 3 3.0 (1.4) 6.0 (3.8) 0.176 Late side effects:† GU ≥ grade 2 3.5 19.2 <0.001 GU grade 3 0.5 5.6 0.006 Urethral stricture 0 11 (7) NR * GU = genitourinary † 3-year actuarial risk Values are number (%) or % unless otherwise noted.
(Wong et al 2009) Single centre, US Accrual: May 1993 – July 2004	Retrospective cohort Level III-2 interventional evidence Downs and Black quality score: **19/27** Overall quality assessment: **Moderate**	**N:853** consecutive patients with localised prostate cancer* LDRBT n 225 Clinical stage: T1 197 (88) T2 28 (12) PSA ≤10, ng/mL 193 (86) Gleason score ≤ 6 173 (77)	**Maximum achieved RTOG acute genitourinary side effects (< 3 months following treatment)** GRADE (%) 0 1 2+* p (chi-square) Grade *3* 3D-CRT (%) 38 22 40 <0.0001 1 IMRT (%) 27 22 52 3 LDRBT (%) 11 14 74 6 **Maximum achieved RTOG late genitourinary side effects (> 3 months**

Study	Study design and quality appraisal	Population	Urinary function
		Adjuvant hormone treatment 153 (68) Low-risk: 158 (70) 3D-CRT IMRT n 270 314 Clinical stage: T1 120 (44) 231 (74) T2 123 (46) 69 (22) PSA ≤, ng/mL 192 (71) 238 (76) Adjuvant hormone treatment 47 (17) 114 (36) Low-risk 119 (44) 109 (35) Loss to follow-up: none evident. Values are n (%). * See study profile for further details.	**following treatment)** GRADE (%) 0 1 2+* p (chi-square) grade *3* 3D-CRT (%) 66 13 21 <0.0001 5 IMRT (%) 47 22 32 5 LDRBT (%) 23 14 63 18 * Grade 3 side effects are combined with grade 2 to prevent small numbers in cells for chi-square test. Importantly, grade 3 late side effects were 18% among LDRBT men compared to 5% among both 3D-CRT and IMRT men. Treatment for urethral stricture among 3D-CRT and IMRT patients occurred in about 2% of cases, compared with 14% of cases among LDRBT patients.
(Buron et al 2007) Multicentre, France Accrual: March 2001 – June 2002	Prospective cohort Level III-2 interventional evidence Downs and Black quality score: **17/27** Overall quality assessment**: Moderate**	**N: 435** men with low-risk prostate cancer from 11 French hospitals treated with LDRBT (308) or RP (127) RP LDRBT Age (years) 62.7±6 65.2±6.3 Neoadjuvant hormones (%) 6.3 43.5 IPSS 7.8 5.9 Loss to follow-up after 24 months was between 35% and 59% (n data not provided) depending on treatment arm—see study profile for further details. Values are mean±standard deviation, unless otherwise specified.	**Urinary outcomes, EORTC QLQ-PR25** RP (n=127) LDRBT (n=308) Urinary incontinence worse than baseline, %: Immediately post-treatment 68.4 12.7 24 months 49.0 19.7 Urinary urgency worse than baseline, %: 2 months 31.4 63.9 24 months 26.5 37.9 Urinary pain worse than baseline, %: 2 months 18.4 63.7

Study	Study design and quality appraisal	Population	Urinary function
			24 months 2.1 19.0 Increased diurnal urination, %: 2 months 34.9 66.0 24 months 16.3 36.8 Increased nocturnal urination, %: 2 months 34.4 62.8 24 months 14.3 30.8 Note: p-values not provided; main in-text data summarised as no other exact values could be determined from the graphical presentation of results.
(Ferrer et al 2008) Multicentre, Spain Accrual: April 2003 – March 2005	Prospective cohort Level III-2 interventional evidence Downs and Black quality score: **17/27** Overall quality assessment: **Moderate**	**N: 841** organ-confined prostate cancer patients RP EBRT LDRBT Age, years 64±5.5 69.2±5.5 66.9±6.5 PSA, ng/mL 7.9±3.3 10.1±7.9 6.9±2.3 Gleason score 6.8±6.2 6±1.1 5.7±4.4 Values are mean±standard deviation. Loss to follow-up: 614 patients treated with LDRBT (275), RP (134) and EBRT (205) were included in HRQoL analysis.	**Mean±SD prostate specific HRQoL (urinary) scores at 2-year follow-up for low-risk patients by treatment group** RP EBRT LDRBT AUA-7† 5.9±6.2 5.38±5.2 5.83±5.3 EPIC urinary:* 87.7±13.8 94±11.2 91.9±11.6 Urinary irritative 96.4±10.3 94.8±10.1 92.7±10.8 Urinary incontinence 78.3±23.1 93.2±13.9 92.7±15.2 **p-values for one-way comparison of HRQoL scores:** RP vs EBRT RP vs LDRBT LDRBT vs EBRT AUA-7 NS NS NS EPIC urinary: <0.001 <0.001 NS Urinary irritative NS 0.005 NS Urinary incontinence <0.001 <0.001 NS † AUA-7 (American Urological Association Symptom Index) assesses obstructive symptoms and ranges from 0 to 35, with higher scores indicating worse function/symptoms.

Study	Study design and quality appraisal	Population	Urinary function
			* All EPIC items were answered on a 5-point Likert scale and transformed linearly to a scale of 0–100, with higher scores indicating better HRQoL.
(Hashine et al 2008) Single centre, Japan Accrual: January 2003 – July 2005	Prospective cohort Level III-2 interventional evidence Downs and Black quality score: **17/27** Overall quality assessment: **Moderate**	**N: 213** (131 RP and 82 LDRBT patients) Age, years* (range): RP 68.0 (42–78); LDRBT 70.5 (50–85); p-value 0.016 PSA, ng/mL*: RP 9.6; LDRBT 6.7; p-value <0.001 Gleason score, n: p-value <0.001 5–6: RP 44; LDRBT 51 7: RP 42; LDRBT 27 8–10: RP 36; LDRBT 4 Neoadjuvant hormones: RP 8; LDRBT 18; p-value 0.002 Nerve-sparing: RP 22; LDRBT - EBRT: RP -; LDRBT 1 * Values are median.	**UCLA-PCI scores** (mean±SD)* Urinary function: (RP / LDRBT / p-value†) baseline: 88.9±19.4 / 94.1±13.9 / 0.027 1 month: 45.2±28.6 / 89.7±16.7 / <0.001 3 months: 60.2±27.5 / 89.9±18.5 / <0.001 6 months: 69.7±27.0 / 92.4±16.3 / <0.001 12 months: 74.6±24.7 / 94.4±12.7 / <0.001 Urinary bother: baseline: 85.4±22.6 / 89.8±20.9 / 0.075 1 month: 59.3±31.5 / 78.1±29.2 / <0.001 3 months: 72.7±28.4 / 75.0±28.5 / 0.585 6 months: 80.4±26.0 / 84.8±22.5 / 0.441 12 months: 84.8±22.5 / 90.0±21.0 / 0.041 * All UCLA-PCI scores were transformed to a scale of 0–100, with higher scores representing better HRQoL. † Mann-Whitney U test
(Pickles et al 2010) Multicentre, Canada Accrual: July 1998 – January 2001	Retrospective cohort Level III-2 interventional evidence Downs and Black quality score: **17/27** Overall quality assessment: **Moderate**	**N: 278** (139 LDRBT, 139 matched EBRT) Age, years: LDRBT 64; EBRT 71 PSA, ng/mL: LDRBT 5.6; EBRT 6.4 Gleason score, %: ≤ 6: LDRBT 87.8; EBRT 87.8 7: LDRBT 12.2; EBRT 12.2 ADT use, %: LDRBT 31.7; EBRT 30.2 Radiation dose, Gy: LDRBT 144; EBRT 68	**Side effects and catheter use** Patients requiring catheterisation: LDRBT 15; EBRT 0; p-value <0.001 Patients with catheter removed after: less than 1 week: LDRBT 52; EBRT NA† more than 1 month: LDRBT 42; EBRT NA Acute grade 3 GU side effects: LDRBT 2.9; EBRT 0.7 Prevalence of late

<table>
<tr><th>Study</th><th>Study design and quality appraisal</th><th>Population</th><th>Urinary function</th></tr>
<tr><td></td><td></td><td>Values are median unless otherwise specified.</td><td>grade 2 GU side effects:*
2 years 13–14 3–4
3 years 11–12 5–6
4 years 7 2–3
5 years 6–7 0
Overall NR‡ NR <0.001

Values are % or p-values as indicated.
* Data are estimates from graphical presentation of results in study.
† Not applicable
‡ Although percentages were not reported, it was stated that genito-urinary (GU) side effects were greater for LDRBT than for EBRT; the p-value is reported accordingly.</td></tr>
<tr><td>(Smith et al 2010)
Population-based, NSW, Australia
Accrual: October 2000 – May 2003</td><td>Prospective cohort
Level III-2 interventional evidence
Downs and Black quality score: 17/27
Overall quality assessment: Moderate</td><td>N: 4542 men (31,95 with histologically confirmed T1a–2c prostate cancer and 1,347 controls with no diagnosis of prostate cancer, as indicated and cross-checked by registry data)
All potential participants had to be physically and mentally capable of a 30-minute telephone interview in English.
Cases, n Controls, n
Potentially eligible 3,195 1,347
Final analysis 1,636 495
AS 200 NA
RP 981 NA
EBRT 123 NA
Combined EBRT/ADT 166 NA
LDRBT 58 NA
Mean age, years [95% CI] 61.2 [60.7, 61.7] 61.2 [61, 61.5]</td><td>Unadjusted mean urinary function (score range 0–100; higher scores indicate better function)
Baseline 3 years
AS 85.7±19.7 91.6±14.7
Nerve-sparing RP 95.6±10.7 85.5±17.0
Non-nerve-sparing RP 94.2±12.4 83.3±19.2
EBRT 92.9±13.8 92.6±15.2
Combined EBRT/ADT 90.7±15.1 89.9±16.5
LDRBT 96.8±7.2 93.5±14.3
Controls 95.2±11.8 95.4
Unadjusted mean urinary bother (score range 0–100; higher scores indicate better function)
Baseline 3 years
AS 58.3±36.4 84.1±14.7
Nerve-sparing RP 80.5±28.5 84.8±23.5
Non-nerve-</td></tr>
</table>

Study	Study design and quality appraisal	Population	Urinary function
			sparing RP 80.6±28.6 83.1±25.3 EBRT 77.2±30.2 81.4±27.6 Combined EBRT/ADT 69.9±35.3 79.3±28.5 LDRBT 80.6±26.9 84.4±24.6 Controls 89.2±22.6 89.7 **Urinary incontinence, n (%)** Baseline 3 years AS 12 (6.0) 6 (3.4) RP 11.1 (1.1) 111 (12.3) EBRT 0 (0.0) 3 (2.7) Combined EBRT/ADT 5 (3.0) 6 (3.9) LDRBT 0 (0.0) 3 (7.0) Controls 5 (1.0) NA† † Controls were not asked the relevant questions at year 3.
(Frank et al 2007) Radiation oncology department, US Accrual: 1998–2000	Retrospective cohort Level III-2 interventional evidence Downs and Black quality score: **16/27** Overall quality assessment: **Moderate**	**N: 960** men treated with LDRBT (160), RP (400) and HDR EBRT (400) LDRBT RP EBRT Age, years 64 61 68 Values are median. Loss to follow-up: 625/960 (65%) in total completed a survey, of whom 443 were found to have undergone monotherapy and so were included in the analysis—see study profile for further details.	**EPIC domain specific prostate cancer HRQoL scores†** (mean±SD) [95% CI] LDRBT EBRT RP Urinary function 85.8±24.3 [80.1,91.4] 90.1±15.3 [87.5,92.7] 83.7±15.8 [81.7,85.7] Urinary bother 78±19.6 [73.5,82.6] 80.4±18 [77.4,83.5] 83.2 ±16.1 [81.1,85.3] Incontinence 85.9±23 [80.6,91.2] 85.5±18.9 [82.3,88.7] 73.4±25.1 [70.2,76.6] Irritation 79.6±19 [75.2,84] 85.2±12.8 [83,87.4] 88.2±11 [88.4,91.4] No statistical difference in urinary function observed between LDRBT and EBRT or RP (p=0.38 and 0.09 respectively). No statistical difference in urinary bother between LDRBT and EBRT of RP (p-values not specified).

<table>
<tr><th>Study</th><th>Study design and quality appraisal</th><th>Population</th><th>Urinary function</th></tr>
<tr><td></td><td></td><td></td><td>RP patients had significantly worse urinary incontinence than LDRBT patients (p<0.001), while no difference observed between LDRBT and EBRT.
LDRBT caused significantly more urinary irritation than RP (p<0.001) and EBRT (p<0.01).
† Higher scores indicate better HRQoL outcomes (scale 0–100).</td></tr>
<tr><td>(Guedea et al 2009)
Single centre, Spain
April 2003 – March 2005</td><td>Prospective cohort
Level III-2 interventional evidence
Downs and Black quality score: 16/27
Overall quality assessment: Moderate</td><td>N: 304 men with prostate cancer
<table>
<tr><th></th><th>LDRBT</th><th>RP</th><th>EBRT</th></tr>
<tr><td>n</td><td>56</td><td>114</td><td>143</td></tr>
<tr><td>Age, years</td><td>67.5</td><td>63.9</td><td>68.8</td></tr>
<tr><td>PSA, ng/mL</td><td>6.4</td><td>7.9</td><td>11.9</td></tr>
<tr><td>Gleason score</td><td>5.7</td><td>6.3</td><td>6.4</td></tr>
</table>
Values are mean and n as indicated.</td><td>Baseline EPIC scores†, mean±SD
<table>
<tr><th></th><th>RP</th><th>EBRT</th><th>LDRBT</th></tr>
<tr><td>Urinary irritation/ obstruction</td><td>94.6±9.4</td><td>96±7.7</td><td>95.2±8.8</td></tr>
<tr><td>Urinary incontinence</td><td>96.1±12.3</td><td>95.5±11.3</td><td>98.5±6.5</td></tr>
</table>
(no statistical difference between baseline scores)

Change in EPIC score at 2 years post treatment, mean±SD
<table>
<tr><th></th><th>RP</th><th>EBRT</th><th>LDRBT</th></tr>
<tr><td>Urinary irritation/ obstruction</td><td>0.01±14.6</td><td>–2.5±13.0</td><td>–7.9±21.5</td></tr>
<tr><td>Urinary incontinence</td><td>–26.9±30.9</td><td>–3.9±16.2</td><td>–12.4±22.1</td></tr>
</table>
Comparison of EPIC scores by treatment after 2 years
<table>
<tr><th></th><th>Urinary irritation/ obstruction, p-value</th><th>Urinary incontinence, p-value</th></tr>
<tr><td>LDRBT vs RP</td><td><0.001</td><td><0.05</td></tr>
<tr><td>RP vs EBRT</td><td>NR</td><td><0.05</td></tr>
<tr><td>LDRBT vs EBRT</td><td>NR</td><td>NR</td></tr>
<tr><td>All groups§</td><td></td><td><0.001</td></tr>
</table>
§ ANOVA

Change in EPIC score at 2 years post treatment, multivariate generalised estimating equation (GEE) model‡, mean±SD
<table>
<tr><th></th><th>RP</th><th>EBRT</th><th>LDRBT</th></tr>
</table></td></tr>
</table>

Study	Study design and quality appraisal	Population	Urinary function
			Irritative/obstructive 4.76±2.11 1.51±2.09 (reference) Urinary incontinence –11.45±4.02 2.37±3.86 (reference) **Comparison of EPIC treatment scores after 2 years, GEE model** Urinary irritation/ obstruction, p-value / Urinary incontinence, p-value LDRBT vs RP 0.025 0.005 RP vs EBRT NR NR LDRBT vs EBRT NR NR † EPIC scores range 0–100, with higher scores indicating better HRQoL. ‡ Adjusting for age, baseline scores, risk group and hormonal treatment, at 2 years post treatment. Values are mean±SD unless otherwise indicated.
(Wei et al 2002) Single centre, US Accrual: June 1995 – May 1999	Retrospective cohort Level III-2 interventional evidence Downs and Black quality score: **16/27** Overall quality assessment: **Moderate**	**N: 1,014** including 142 male controls who are not further considered‡ LDRBT n 112 Age, years 67.2±7.3 Time since primary therapy, months 21 Adjuvant/ neoadjuvant therapy, % 51 PSA, ng/mL 9.7±14.9 Gleason score, %: 2–6 68.3 7 23.2 8–10 8.5 EBRT RP	**EPIC* urinary scores for follow-up exceeding 1 year** LDRBT EBRT RP Urinary irritative 71.5†# [67.4,75.5] 84.2†‡ [81.2,87.2] 89.6#‡ [88.3,91.1] Urinary incontinence 82.1 [74.4,89.9] 92.8† [87.1,98.5] 77.5† [75,80.1] * Expanded Prostate Cancer Index, values are mean [99% CI]. Multivariable modelling was used to adjust for age, time since therapy, Gleason score, clinical stage, PSA and use of hormonal therapy. † # ‡ Values that share a common symbol were significantly different in a pairwise comparison (significance set at 0.008 after Tukey adjustment for comparisons between three groups), p<0.0005.

Study	Study design and quality appraisal	Population			Urinary function			
		n	203	896				
		Age, years	70.9±7.2	63.5±7.8				
		Time since primary therapy, months	29	30				
		Adjuvant/ neoadjuvant therapy, %	33	28				
		PSA, ng/mL	9.1±12.7	7.3±7.2				
		Gleason score, %:						
		2–6	43.1	59.6				
		7	47.9	37.3				
		8–10	9.0	3.1				
		Values are median±SD, except where indicated.						
		‡ A control group used in the primary analysis was not considered given that a secondary analysis made direct comparison between treatment modalities, in accordance with inclusion criteria for this assessment.						
(Kirschner-Hermanns et al 2008) Single institution, Germany Accrual: January 1999 – December 2002	Prospective cohort Level III-2 interventional evidence Downs and Black quality score: **15/27** Overall quality assessment: **Poor**	**N: 94** (33 LDRBT, 61 RP patients)			**Urinary symptoms after 1 year, percentage of patients**			
				RP		BT	RP	p (chi-square)*
		Age, years (range)†		64 (54–75)	LUTS	88	80	0.352
		PSA, ng/mL†		9.2 (1.6–55.6)	Bothersome LUTS	30	11	0.024
		Gleason score†		5 (3–8)	Urgency	88	64	0.013
		OCO*		0.78 (0.08–2.67)	Bothersome urgency	21	2	0.001
		Max flow < 10 mL/s, %		30	Incontinence	52	66	0.183
		Residual vol > 50 mL, %		34#	Bothersome incontinence	24	11	0.183
		Max capacity < 200 mL, %		15	Stress incontinence	18	53	0.001
				LDRBT	Bothersome stress incont.	-	11	-
					Have to wear pads	10	41	0.001
					Have to wear >2 pads / day	0	6	0.133

<table>
<tr><th>Study</th><th>Study design and quality appraisal</th><th>Population</th><th>Urinary function</th></tr>
<tr><td></td><td></td><td>Age, years (range)† 67 (57–75)
PSA, ng/mL† 7.7 (3.2–17.0)
Gleason score† 5 (2–7)
OCO* 0.74 (0.34–1.70)
Max flow < 10 mL/s, % 21
Residual vol > 50 mL, % 12#
Max capacity < 200 mL, % 6

† Median (range)
* Obstruction coefficient
# Chi-square, p=0.019 (RP cf LDRBT)</td><td></td></tr>
<tr><td>(Pinkawa et al 2009)
Single centre, Germany
Accrual: 2003–06</td><td>Comparison of two matched single arms
Level III-3 interventional evidence
Downs and Black quality score: 16/27
Overall quality assessment: Moderate</td><td>N: 104 (52 in each group)
LDRBT / EBRT
Age, years (range) 68 (51–77) / 68 (48–77)
PSA, ng/mL 7 (1.5–14) / 8 (2.5–24)
Gleason score < 7, n (%) 50 (96) / 39 (75)
Neoadjuvant hormones, n (%) 14 (27) / 14 (27)
Values are median (range) unless otherwise specified.</td><td>Mean (quartiles) function and bother scores from the EPIC questionnaire†
Time A§ / Time B / Time C
Urinary bother:
EBRT 83‡ (68;89;96) / 65 (47;64;86) / 88 (83;93;96)
LDRBT 90 (86;93;100) / 57 (37;61;71) / 82 (68;89;100)
Urinary incontinence bother:
EBRT 94 (100;100;100) / 80 (75;100;100) / 92 (100;100;100)
LDRBT 97 (100;100;100) / 71 (25;100;100) / 86 (94;100;100)
Urinary obstructive/ irritative bother:
EBRT 82 (79;87;95) / 64 (46;63;80) / 87 (80;90;100)
LDRBT 90 (85;95;100) / 57 (41;58;70) / 82 (66;87;100)
§ Time A = before LDRBT/EBRT, Time B = 1 month after LDRBT / on the last day of EBRT, Time C = median 16 months after LDRBT/EBRT.</td></tr>
</table>

Study	Study design and quality appraisal	Population	Urinary function
			‡ Italics indicate significant differences between treatment groups. Quartiles = 25th, 50th, 75th percentiles. **Comparison of function and bother scores from the EPIC questionnaire** Time A vs B, p-value / Time A vs C, p-value Urinary bother: EBRT <0.01 <0.05 LDRBT <0.01 <0.01 Urinary incontinence bother: EBRT <0.01 NS LDRBT <0.01 <0.01 Urinary obstructive/ irritative bother: EBRT <0.01 NS LDRBT <0.01 <0.01 **Selected symptoms from the EPIC questionnaire** Time A (%) / Time B (%) / Time C (%) ≥ 1 pad to control urinary leakage: EBRT 6 4† 4 LDRBT 0 17 10 Moderate/big problem from dripping/ leaking urine: EBRT 4 16 6 LDRBT 2 28 12 Moderate/big problem from pain on urination: EBRT 2 26 0† LDRBT 2 37 10 † p<0.05 (responses in EBRT group are significantly different than in the

Study	Study design and quality appraisal	Population	Urinary function
			LDRBT group). † EPIC scale 0 to 100, with higher scores indicating better HRQoL.
(Bucci et al 2002)	Case series Level IV interventional evidence NHMRC case series quality score: **6/6** Overall quality assessment: **Good**	**N: 282** Age, years Median (range) = 66 (38–78) Clinical stage T1c–T2b Gleason score ≤ 7 (3+4 only) PSA, ng/mL, %: ≤ 10 82% 10 – ≤ 15 12%	Catheterisation rate following LDRBT = 15% (n=43) Median duration of catheterisation = 21 days (1–365) Higher IPSS at baseline were associated with higher rates of catheterisation.
(Crook et al 2008) Single centre, Canada Accrual: March 1999 – July 2005	Case series Level IV interventional evidence NHMRC case series quality score: **6/6** Overall quality assessment: **Good**	**N: 484** Age, years Mean (SD) = 63.1 (6.9) Clinical stage T1c–T2a Gleason score ≤ 6 PSA ≤ 10 ng/mL	An increase in IPSS (scale 0–35) of more than 5 points to a total score of more than 15 points was reported in 23%. Of those with raised IPSS, 30% remained raised for more than 6 months. Some urgency or urge incontinence was diagnosed in 6.4% of men; 3.9% required medication for urgency or urge incontinence. In those whose symptoms resolved, median duration was 12 months; 0.8% of men had ongoing symptoms at the end of the study. 13 men (2.7%) required catheterisation after 1 year following treatment; 8 of 18 men required catheterisation due to urethral stricture.
(Sacco et al 2003) Single centre, Israel Accrual: September 1996 – October 2001	Case series Level IV interventional evidence NHMRC case series quality score: **6/6** Overall quality assessment: **Good**	**N: 400** consecutive patients with early stage prostate cancer Age, years Median (range) = 65 (41–70) Clinical stage T1c: 73%, > T2a: 27% Gleason score 98% of patients ≤ 7 PSA 91% of patients ≤ 10 ng/mL Loss to follow-up: 3 patients	Number of patients who developed acute urinary retention requiring catheterisation: 45 (11.3%) Median number of days to development of acute urinary retention requiring catheterisation: 12 Median (range) duration of catheterisation, days: 14 (1–365) Proportion of patients with acute urinary retention among those who did and did not use corticosteroids (dexamethasone): 8.2% vs 18.8%, respectively, p=0.006 Number of patients with gross haematuria: 2

Study	Study design and quality appraisal	Population	Urinary function
(Keyes et al 2009) Multicentre, Canada Accrual: July 1998 – June 2003	Case series Case series Level IV interventional evidence NHMRC case series quality score: **5/6** Overall quality assessment: **Good**	**N: 712** eligible from 932 consecutive patients Age, years Median (range) = 65.5 (46–82) Clinical stage <T2c Gleason score ≤ 7 PSA, ng/mL, %: ≤ 10 85.8% 10 – ≤ 15 14.2% Follow-up at least 34 months: 144 excluded due to living in remote area, 35 less than 34 months follow-up, 41 with insufficient data.	An increase in IPSS (scale 0–35) of more than 5 points greater than post-treatment nadir was reported in 53.2%; 66% of IPSS flare had resolved in 6 months, 90% had resolved in 1 year. Note: overlapping population with Bucci 2002 (above)—different outcomes reported
(Mabjeesh et al 2007) Single centre, Israel Accrual: June 1998 – June 2006	Case series Level IV interventional evidence NHMRC case series quality score: **5/6** Overall quality assessment: **Good**	**N: 655** Age, years Mean±SD = 67.3±6.5 Clinical stage T1 – T2c Gleason score 99.9% of patients ≤ 7 PSA Mean±SD = 7.75±3.45 ng/mL Loss to follow-up: None apparent	Number of patients with urinary retention requiring catheterisation: 21 Median (range) days to onset of urinary retention requiring catheterisation: 1 (1–60) Median duration of catheterisation, months (range): 6.25 (2–24) Number of patients with urethral stricture: 1
(Matzkin et al 2003) Single centre, Israel Accrual: not reported	Case series Level IV interventional evidence NHMRC case series quality score: **5/6** Overall quality assessment: **Good**	**N:300** Group 1: 136 preplanned Group 2: 164 intraoperatively planned Age, years: G1: Mean 67.2 G2: Mean 68.4 Clinical stage ≤ T2 Gleason score ≤ 6	No patient experienced urinary incontinence following implantation. Five patients experienced 'prolonged' urinary retention, with three requiring a transurethral resection of the prostate. For the pre-planned group, IPSS returned to normal (±1 point) for 92% of men by 12 months following treatment. For the intra-operatively planned group, IPSS returned to normal for 95% of men by 18 months.

Study	Study design and quality appraisal	Population	Urinary function
		PSA, ng/mL: G1: Mean 8.69 G2: Mean 7.95	
(Mitchell et al 2008) Multicentre, UK Accrual: January 2003 – October 2006	Case series Level IV interventional evidence NHMRC case series quality score: **5/6** Overall quality assessment: **Good**	**N: 1,535** men treated with permanent seed BT Age, years, median (range): Centre 1: 63 (43–79) Centre 2: 65 (40–79) Centre 3: 63 (43–82) Clinical stage T1c–T3a Gleason score > 97% of patients ≤ 7 PSA ≤ 7 ng/mL Loss to follow-up: NA, complete reporting for all patients registered on database	Median IPSS* for patients at all centres increased from a baseline value of 5, peaked at 18 after 6 weeks, and was not significantly different from baseline at 12 months. Median duration of catheterisation was 53, 18 and 53 days at centres 1, 2 and 3 respectively. Urethral stricture rates were 1% at all centres. * International Prostate Symptom Score, scale = 0–35
(Stone et al 2010) Single centre, US Accrual: 1990 –2006	Case series Level IV interventional evidence NHMRC case series quality score: **5/6** Overall quality assessment: **Good**	**N: 395** Age, years Mean 68.9 (SD±6.8) Clinical stage T1b–T3a Gleason score ≤ 7 98.2% PSA, ng/mL: ≤ 10 83.3% 10 – ≤ 20 14.4% > 20 2.3% Prostate volume > 50 cc 85% of men were treated with ^{125}I LDRBT.	9.3% of men suffered urinary retention following ^{125}I LDRBT (n=31) lasting a median of 42 days.
(Zelefsky et al 2007a) Single centre, US Accrual: January 1998 – December 2004	Case series Level IV interventional evidence NHMRC case series quality	**N:562** Age Not reported Clinical stage	NCI CTCAE urinary side effects: late grade 2 17% late grade 3 3%

Study	Study design and quality appraisal	Population	Urinary function
	score: **5/6** Overall quality assessment: **Good**	99.8% ≤ T2 Gleason score 99.8% ≤ 7 PSA, ng/mL, %: ≤ 10 94.5% 10 – ≤ 20 5.3% > 20 0.2%	NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events
(Kao et al 2008) Single centre, US Accrual: June 1995 – February 2005	Case series Level IV interventional evidence NHMRC case series quality score: **4/6** Overall quality assessment: **Moderate**	**N: 643** men with localised prostate cancer Age Not reported Clinical stage T1a–T2c Gleason score 98.8% of patients ≤ 7 PSA Median = 6.1 ng/mL Loss to follow-up: Urinary outcomes were available for 249 patients.	Median IPSS* increased from a baseline value of 6, peaked at 18 after 6 months and was not significantly different from baseline at 12 months. Acute urinary retention occurred in 12.4% of patients. Patient reported urinary QoL was unchanged before and after implantation. * International Prostate Symptom Score, scale = 0–35
(Eckman et al 2010) Single centre, US Accrual: 1995–2007	Case series Level IV interventional evidence NHMRC case series quality score: **3/6** Overall quality assessment: **Moderate**	**N: 394** Age, years Mean 67.3 (SD±7.6) Clinical stage 99.5% < T3 Gleason score 95.7% < 8 PSA Mean 7.7 (SD±4.7) ng/mL 2.8% received adjuvant EBRT.	In men who received LDRBT between 1993 and 1997, catheterisation for urinary retention was 10%. Following 1997, catheterisation rates dropped to 2%. Following 1997, dexamethasone (6 mg) intraoperatively and the use of alpha blockers after implantation was introduced (precise numbers not reported). Urinary symptoms were common following implantation in men who did not have the symptom before treatment. Frequency: Month 3 % (95% CI) 33.5 (28.3–39.3); Median time to resolution (months) 12 (10–14) Hesitancy: 22.4 (18.1–27.4); 12 (9–14) Urgency: 42.0 (35.7–48.6); 14 (11–17) Decreased force: 40.3 (34.7–46.2); 10 (8–12) Haematuria: 3.7 (2.1–6.2); not recorded

Study	Study design and quality appraisal	Population	Urinary function
			Nocturia 32.4 (27.3–37.9) 10 (8–12) Dysuria 31.6 (27–36.5) 9 (8–10) Medication 27.5 (23.8–31.6) 30 (25–34) Values are mean estimates (95% CI) from logistic regression models using generalised estimating equation methods to account for within-subject correlation—estimates are of men who did not report the particular symptom at baseline.
(Elshaikh et al 2003) Single centre, US Accrual: 1996–2001	Case series Level IV interventional evidence NHMRC case series quality score: **3/6** Overall quality assessment: **Moderate**	**N: 402** Age, years Median 69 Clinical stage ≤ T2 Gleason score (range) Median 6 (4–8) PSA Median 6.45 ng/mL	Intermittent self-catheterisation for urinary retention was reported in 44 men (10.9%) for a median duration of 6 weeks. Three patients eventually underwent transurethral resection of the prostate for prolonged urinary retention (> 10 months).
(Schafer et al 2008) Single centre, Germany Accrual: June 1998 – December 2003	Case series Level IV interventional evidence NHMRC case series quality score: **2/6** Overall quality assessment: **Poor**	**N: 258** (296 treated consecutively, 38 patients died before assessment) Age, years Median 71 Clinical stage 94% ≤ T2 Gleason score: ≤ 7 71% ≥ 8 0.4% Unknown 28.6% PSA Median 7.3 ng/mL	16% of men used pads for urinary incontinence at a median of 51 months post implantation. 9.3%, 3.6%, 2.6% and 0.5% used one, two, three and four or more pads per day.

Table notes:
3D-CRT = three-dimensional conformal radiotherapy; ADT = androgen deprivation therapy; EBRT = external beam radiotherapy; EORTC QLQ-PR25 = European Organisation for Research and Treatment of Cancer quality of life questionnaire – prostate cancer module; EPIC = Expanded Prostate cancer Index Composite; HRQoL = health-related quality of life; IMRT = intensity modulated radiotherapy; IPSS = International Prostate Symptom Score; LDRBT = low-dose-rate brachytherapy ; LUTS = lower urinary tract symptoms; NR = not reported; NS = not significant; RP = radical prostatectomy; RTOG = Radiation Therapy Oncology Group; UCLA-PCI = University of California, Los Angeles – Prostate Cancer Index

Appendix E Data tables for bowel side effects

Table 32 Bowel side effects resulting from low-dose-rate brachytherapy, radical prostatectomy, external beam radiotherapy and active surveillance for the treatment of localised prostate cancer

Study	Study design and quality appraisal	Population	Bowel function
(Giberti et al 2009) Single centre, Italy Accrual: May 1999 – October 2002	Randomised controlled trial Level II interventional evidence Downs and Black quality score: **19/27** Overall quality assessment: **Moderate**	**N: 100** RP patients and **100** LDRBT patients Questionnaires were completed for 89 RP patients and 85 LDRBT patients. Exclusion criteria were in accordance with American Brachytherapy Society. RP / LDRBT No. patients: 100 / 100 Age, years: 65.2 (57–74) / 65.6 (56–74) Gleason score: 5.9 / 5.7 PSA, ng/mL: 7.8 (3.5–10.0) / 7.5 (2.9–9.3) Values are mean (range) unless otherwise indicated.	**Mean scores from questionnaires at four time points** (higher scores indicate worse function/symptoms Pre-treatment / 6 months / 1 year / 5 years EORTC-QLQ-PR25: Bowel symptoms RP: 2 / 3 (NS)* / 2 (NS) / 2 (NS) LDRBT: 2 / 6 (0.03) / 4 (NS) / 5 (NS) EORTC-QLQ: Constipation RP: 3 / 4 (NS) / 4 (NS) / 3 (NS) LDRBT: 1 / 2 (NS) / 1 (NS) / 0 (NS) Diarrhoea RP: 4 / 4 (NS) / 6 (NS) / 5 (NS) LDRBT: 5 / 6 (NS) / 8 (NS) / 6 (NS) * p-values for change from pre-treatment value
(Eade et al 2008) Single centre, US LDRBT patients: May 1998 – August 2004 EBRT patients: August 2001 – June 2004	Prospective cohort Level III-2 interventional evidence Downs and Black quality score: **19/27** Overall quality assessment**:** **Moderate**	**N: 374** low-risk prostate cancer patients (as defined by American Joint Committee on Cancer) with Gleason score < 7 EBRT / LDRBT n: 216 / 158 Age, years: 67.6 (27–81) / 64.7 (42–78) PSA, ng/mL: 5.2 (0.4–9.6) / 5.2 (0.5–9.8) Values are median (range). No patients were lost to follow-up.	**Bowel outcomes, RTOG scale** EBRT / LDRBT / p-value Acute side effects GI Grade 2: 5.0 (2.3) / 3.0 (1.9) / 1.00 GI Grade 3: 0 / 0 Late side effects* GI Grade 2: 2.4 / 7.8 / 0.028 GI Grade 3: 0 / 0.1 / 0.228 GI = gastrointestinal

Study	Study design and quality appraisal	Population	Bowel function
			Values are number (%) or %, unless otherwise noted. * 3-year actuarial risk
(Wong et al 2009) Single centre, US Accrual: May 1993 – July 2004	Retrospective cohort Level III-2 interventional evidence Downs and Black quality score: **19/27** Overall quality assessment: **Moderate**	**N:853** consecutive patients with localised prostate cancer* LDRBT n 225 Clinical stage: T1 197 (88) T2 28 (12) PSA ≤10 ng/mL 193 (86) Gleason score ≤ 6 173 (77) Adjuvant hormone treatment 153 (68) Low-risk 158 (70) 3D-EBRT / IMRT n 270 / 314 Clinical stage: T1 120 (44) / 231 (74) T2 123 (46) / 69 (22) PSA ≤ ng/mL 192 (71) / 238 (76) Adjuvant hormone treatment 47 (17) / 114 (36) Low-risk 119 (44) / 109 (35) Loss to follow-up: none evident. Values are n (%). * See study profile for further details.	**Maximum achieved RTOG acute gastrointestinal side effects (< 3 months following treatment)** GRADE 0 / 1 / 2+* / p (chi-square) / Grade *3* 3D-CRT (%) 26 / 20 / 54 / <0.0001 / 0 IMRT (%) 28 / 26 / 46 / / 1 LDRBT (%) 77 / 14 / 8 / 0 / **Maximum achieved RTOG late gastrointestinal side effects (> 3 months following treatment)** GRADE 0 / 1 / 2+* / p (chi-square) / Grade *3* 3D-CRT (%) 57 / 26 / 17 / 0.0128 / 2 IMRT (%) 63 / 23 / 15 / / 1 LDRBT (%) 72 / 15 / 13 / / 1 * Grade 3 side effects are combined with grade 2 to prevent small numbers in cells for chi-square test. Four 3D-CRT patients, 2 LDRBT patients and no IMRT patients developed grade 3 proctitis.
(Litwin et al 2004) Multicentre, US	Prospective cohort Level III-2 interventional	**N: 1,584** consecutively recruited prostate cancer patients	**UCLA PCI scores for bowel function and bother** (scale 0–100, with higher scores representing better outcome)*

Study	Study design and quality appraisal	Population	Bowel function
Accrual: Not reported	evidence Downs and Black quality score: **18/27** Overall quality assessment: **Moderate**	RP (n=1276) Age, years 61.2±6.8 Gleason score, %: 2–6 77 7 19 8–10 4 EBRT (n=99) Age, years 70.9±6.1 Gleason score, %: 2–6 67 7 25 8–10 8 LDRBT (n=209) Age, years 68.6±7.4 Gleason score, %: 2–6 89 7 9 8–10 1 Values are mean±SD unless otherwise specified.	RP / EBRT / LDRBT Bowel function: 0 months‡ 75±1.2 / 60±2.1 / 68±2.1 3 months 84±1.2 / 73±2.2 / 77±2.0 6 months 84±1.2 / 75±2.2 / 79±2.1 9 months 85±1.2 / 76±2.2 / 81±2.0 12 months 85±1.3 / 76±2.3 / 78±2.3 15 months 85±1.3 / 78±2.3 / 83±2.2 18 months 85±1.3 / 74±2.4 / 81±2.6 21 months 85±1.3 / 74±2.5 / 85±2.7 24 months 84±1.4 / 78±2.8 / 80±3.3 Bowel bother: 0 months† 74±1.7 / 50±3.0 / 61±3.0 3 months 83±1.8 / 67±3.2 / 76±2.8 6 months 84±1.8 / 70±3.1 / 75±3.0 9 months 84±1.8 / 69±3.2 / 78±2.8 12 months 84±1.8 / 72±3.2 / 78±3.2 15 months 85±1.8 / 71±3.2 / 81±3.1 18 months 85±1.8 / 67±3.4 / 79±3.8 21 months 85±1.9 / 66±3.6 / 83±3.8 24 months 83±2.0 / 73±3.9 / 80±3.9 * Based on 808 questionnaire responses † Between-group comparison ‡ Score as measured immediately after treatment Values are mean±SE.
(Hashine et al 2008) Single centre, Japan Accrual: January 2003 – July 2005	Prospective cohort Level III-2 interventional evidence Downs and Black quality score: **17/27** Overall quality assessment: **Moderate**	**N: 213** (131 RP and 82 LDRBT patients) RP / LDRBT / p-value Age, years* (range) 68.0 (42–78) / 70.5 (50–85) / 0.016 PSA, ng/mL* 9.6 / 6.7 / <0.001 Gleason score, n: / / <0.001 5–6 44 / 51	**UCLA-PCI scores** (mean±SD)* RP / LDRBT / p-value† Bowel function: Baseline 89.8±19.5 / 84.9±18.1 / 0.055 1 month 78.7±16.3 / 82.8±20.8 / 0.032 3 months 83.2±16.5 / 84.1±18.6 / 0.478 6 months 87.5±15.9 / 83.8±17.4 / 0.276 12 months 86.0±16.7 / 87.5±18.9 / 0.201 Bowel bother:

Study	Study design and quality appraisal	Population	Bowel function
		7 42 27 8–10 36 4 Neoadjuvant hormones 8 18 0.002 Nerve-sparing 22 - EBRT - 1 * Median	Baseline 90.8±17.9 91.1±17.2 0.913 1 month 84.0±22.6 85.4±22.9 0.580 3 months 88.8±20.8 85.5±17.8 0.081 6 months 93.6±15.3 81.8±22.8 0.002 12 months 93.6±16.2 90.4±18.8 0.188 * All UCLA-PCI scores were transformed to a scale of 0–100, with higher scores representing better HRQoL. † Mann-Whitney U test
(Buron et al 2007) Multicentre, France Accrual: March 2001 – June 2002	Prospective cohort Level III-2 interventional evidence Downs and Black quality score: **17/27** Overall quality assessment**:** **Moderate**	**N: 435** men with low-risk prostate cancer from 11 French hospitals treated with LDRBT (308) or RP (127) RP LDRBT Age, years 62.7±6 65.2±6.3 Neoadjuvant hormones, % 6.3 43.5 IPSS 7.8 5.9 Values are mean±standard deviation. Loss to follow-up after 24 months was between 35% and 59% (n data not provided) depending on treatment arm—see study profile for further details. Values are mean±standard deviation, unless otherwise specified.	**Bowel outcomes, EORTC QLQ-PR25** RP LDRBT Faecal incontinence worse than baseline, % 24 months 2 8.9 More rectal bleeding than baseline, % 24 months 0 15.1 Note: p-values not provided; main in-text data summarised as no other exact values could be determined from the graphical presentation of results.
(Ferrer et al 2008) Multicentre, Spain Accrual: April 2003 – March 2005	Prospective cohort Level III-2 interventional evidence Downs and Black quality score: **17/27** Overall quality assessment: **Moderate**	**N: 841** organ-confined prostate cancer patients RP EBRT LDRBT Age, years 64±5.5 69.2±5.5 66.9±6.5 PSA, ng/mL 7.9±3.3 10.1±7.9 6.9±2.3 Gleason score 6.8±6.2 6±1.1 5.7±4.4 Values are mean±standard deviation. Loss to follow-up: 614 patients treated with LDRBT (275), RP (134)	**Mean prostate specific HRQoL scores at 2-year follow-up for low-risk patients by treatment group** RP EBRT LDRBT EPIC* bowel 98.9±2.3 94.1±11.2 97.7±6 **p-values for one-way comparison of HRQoL scores** RP vs EBRT RP vs LDRBT LDRBT vs EBRT EPIC bowel <0.001 NS <0.001 * All EPIC items were answered on a 5-point Likert scale and transformed

Study	Study design and quality appraisal	Population	Bowel function
		and EBRT (205) were included in HRQoL analysis.	linearly to a scale of 0–100, with higher scores indicating better HRQoL.
(Pickles et al 2010) Multicentre, Canada Accrual: July 1998 – January 2001.	Retrospective cohort Level III-2 interventional evidence Downs and Black quality score: **17/27** Overall quality assessment: **Moderate**	**N: 278** (139 LDRBT, 139 matched EBRT) LDRBT EBRT Age, years 64 71 PSA, ng/mL 5.6 6.4 Gleason score, %: ≤ 6 87.8 87.8 7 12.2 12.2 ADT use, % 31.7 30.2 Radiation dose, Gy 144 68 Values are median unless otherwise specified.	**Side effects** LDRBT EBRT p-value Acute grade 2 GI side effects 4 5 NS† Prevalence of late grade 3–4 GI side effects:* 2 years 6–7 14–15 3 years 5–6 8–9 4 years 3–4 4 5 years 3–4 3–4 Overall NR‡ NR 0.0183 Values are % or p-value as indicated. * Data are estimates from graphical presentation of results in study. † Not significant ‡ Although percentages were not reported, it was stated that GI side effects was greater for EBRT than for LDRBT; the p-value is reported accordingly.
(Smith et al 2010) Population-based, NSW, Australia Accrual: October 2000 – May 2003	Prospective cohort Level III-2 interventional evidence Downs and Black quality score: **17/27** Overall quality assessment: **Moderate**	**N: 4,542** men (3,195 with histologically confirmed T1a–2c prostate cancer and 1,347 controls with no diagnosis of prostate cancer, as indicated and cross-checked with registry data) All potential participants had to be physically and mentally capable of a 30-minute telephone interview in English. Cases, n Controls, n Potentially eligible 3,195 1,347 Final analysis 1,636 495 AS 200 NA RP 981 NA EBRT 123 NA Combined	**Unadjusted mean bowel function** (score range 0–100; higher scores indicate better function) Baseline 3 years AS 83.9±17.9 86.7±16.4 Nerve-sparing RP 89±12.0 88.1±13.9 Non-nerve-sparing RP 87.1±15.7 88.5±12.3 EBRT 86.4±16.5 84.5±15.8 Combined EBRT/ADT 87±14.5 81.8±19.0 LDRBT 91.8±9.3 88.8±11.5 Controls 88.4±12.3 89.8

Study	Study design and quality appraisal	Population	Bowel function
		EBRT/ADT 166 NA LDRBT 58 NA Mean age, years [95% CI] 61.2 [60.7, 61.7] 61.2 [61, 61.5]	**Unadjusted mean bowel bother** (score range 0–100; higher scores indicate better function) Baseline / 3 years AS 84.3±28.3 / 88.1±23.2 Nerve-sparing RP 93±18.4 / 90±20.9 Non-nerve-sparing RP 90.4±22.1 / 90.5±18.7 EBRT 87.6±25.9 / 79.8±28.2 Combined EBRT/ADT 88.1±24.7 / 78.8±29.0 LDRBT 94.4±14.8 / 91.1±14.6 Controls 89.2±23.3 / 93.8 **Moderate or severe bowel problems, n (%)** Baseline / 3 years AS 27 (13.5) / 11 (6.3) RP 43 (4.4) / 32 (3.5) EBRT 13 (10.6) / 16 (14.5) Combined EBRT/ADT 15 (9.0) / 19 (12.5) LDRBT 0 (0.0) / 0 (0.0) Controls 5 (1.0) / NA† † Controls were not asked the relevant questions at year 3.
(Frank et al 2007) Radiation oncology department, US Accrual: 1998–2000	Retrospective cohort Level III-2 interventional evidence Downs and Black quality score: **16/27** Overall quality assessment:	**N: 960** men treated with LDRBT (160), RP (400) and HDR EBRT (400) LDRBT RP EBRT Age, years 64 61 68 Values are median.	**EPIC domain-specific prostate cancer HRQoL scores†** (mean±SD) LDRBT EBRT RP Bowel function 89.4±11.5 [86.8,92.1] / 85.8±14.2 [83.4,88.2] / 93±9 [91.8,94.2] Bowel 86.4±16.8 / 85.1±19.8 / 94.6±10.4

Study	Study design and quality appraisal	Population	Bowel function
	Moderate	Loss to follow-up: 625/960 (65%) in total completed a survey, of whom 443 were found to have undergone monotherapy and included in the analysis—see study profile for further details.	bother [82.5,90.3] [81.7,88.5] [93.2,95.9] LDRBT was associated with significantly worse bowel function than RP (p=0.018); worse bowel function was observed for EBRT than LDRBT (p=0.03). LDRBT was associated with significantly more bowel bother than RP (p<0.001); bowel bother for EBRT and LDRBT was not statistically different. † Higher scores indicate better HRQoL outcomes (scale 0–100).
(Guedea et al 2009) Single centre, Spain April 2003 – March 2005	Prospective cohort Level III-2 interventional evidence Downs and Black quality score: **16/27** Overall quality assessment: **Moderate**	**N: 304** men with prostate cancer LDRBT RP EBRT n 56 114 143 Age, years 67.5 63.9 68.8 PSA, ng/mL 6.4 7.9 11.9 Gleason score 5.7 6.3 6.4 Values are mean and n as indicated	**Baseline EPIC scores†** RP EBRT LDRBT Intestinal summary 98.3±3.3 96.9±7.1 97.1±6 (no statistical difference between baseline scores) **Change in EPIC score at 2 years post treatment** RP EBRT LDRBT Intestinal summary 0.03±6.1 –2.3±9.3 –0.4±9.3 (no statistical difference in changes in score at 2 years) **Change in EPIC score at 2 years post treatment, multivariate generalised estimating equation (GEE) model*** RP EBRT LDRBT Intestinal summary 0.81±1.62 –1.68±1.61 (reference) (no statistical difference in changes in score at 2 years after adjusting for age, risk group, use of hormones and pre-treatment scores) † EPIC scores range 0–100, with higher scores indicating better HRQoL. * Adjusting for age, baseline scores, risk group and hormonal treatment, at 2 years post treatment Values are mean±SD unless otherwise indicated.
(Wei et al 2002) Single centre, US Accrual: June 1995 – May 1999	Retrospective cohort Level III-2 interventional evidence Downs and Black quality	**N: 1,014** including 142 healthy male controls who are not further considered‡ LDRBT n 112	**EPIC* bowel summary scores for follow-up exceeding 1 year** Bowel LDRBT EBRT RP 76†# [72.2,79.8] 85.2†‡ [82.5,87.8] 93.2#‡ [92,94.5]

Study	Study design and quality appraisal	Population	Bowel function
	score: **16/27** Overall quality assessment: **Moderate**	Age, years 67.2±7.3 Time since primary therapy, months 21 Adjuvant/ neoadjuvant therapy, % 51 PSA, ng/mL 9.7±14.9 Gleason score, %: 2–6 68.3 7 23.2 8–10 8.5 EBRT / RP n 203 / 896 Age, years 70.9±7.2 / 63.5±7.8 Time since primary therapy, months 29 / 30 Adjuvant/ neoadjuvant therapy, % 33 / 28 PSA, ng/mL 9.1±12.7 / 7.3±7.2 Gleason score, %: 2–6 43.1 / 59.6 7 47.9 / 37.3 8–10 9.0 / 3.1 Values are median±SD, except where indicated. ‡ A control group of healthy males was unnecessary for data extraction and irrelevant to the research questions of this review.	* Expanded Prostate Cancer Index, values are mean [99% CI]. Multivariable modelling was used to adjust for age, time since therapy, Gleason score, clinical stage, PSA and use of hormonal therapy. † # ‡ Values that share a common symbol were significantly different in a pairwise comparison (significance set at 0.008 after Tukey adjustment for comparisons between three groups), p<0.0005.
(Tsui et al 2005)	Retrospective cohort	**N: 202**	**Bowel symptoms based on RTOG late radiation morbidity scoring**

<table>
<tr><th>Study</th><th>Study design and quality appraisal</th><th>Population</th><th>Bowel function</th></tr>
<tr>
<td>Single institution, Canada
Accrual: 1998–2000</td>
<td>Level III-2 interventional evidence
Downs and Black quality score: 15/27
Overall quality assessment: Poor</td>
<td>
<table>
<tr><th></th><th>LDRBT</th><th>RT</th></tr>
<tr><td>Age, years
Mean±SD</td><td>64.8±6.5</td><td>66.3±5.1</td></tr>
<tr><td>PSA, ng/mL
Mean±SD</td><td>6.2 (2.3)</td><td>9.1 (3.7)</td></tr>
<tr><td>Gleason score, n (%):†</td><td></td><td></td></tr>
<tr><td>≤ 6</td><td>83 (97.6)</td><td>30 (40.5)</td></tr>
<tr><td>7</td><td>2 (2.4)</td><td>41 (55.4)</td></tr>
<tr><td>8</td><td>0 (0)</td><td>3 (4.1)</td></tr>
<tr><td>α-blocker, %</td><td>3.5</td><td>6.6</td></tr>
<tr><td>Neoadjuvant ADT, %</td><td>32.9</td><td>13.2*</td></tr>
</table>
Values are mean±SD unless otherwise specified.
† p<0.001, *p=0.005
</td>
<td>
system*
<table>
<tr><th></th><th>LDRBT†</th><th>EBRT‡</th><th>p-value</th></tr>
<tr><td>Bowel symptoms, %</td><td></td><td></td><td></td></tr>
<tr><td>6 months</td><td>10.9</td><td>12.5</td><td>1.0</td></tr>
<tr><td>12 months</td><td>3.3</td><td>12.1</td><td>0.098</td></tr>
<tr><td>18 months</td><td>5.3</td><td>14.9</td><td>0.21</td></tr>
<tr><td>24 months</td><td>7.1</td><td>14.9</td><td>0.36</td></tr>
<tr><td>30 months</td><td>7.7</td><td>15.0</td><td>0.36</td></tr>
<tr><td>36 months</td><td>19</td><td>4.5</td><td>0.08</td></tr>
<tr><td>42 months</td><td>0</td><td>10.8</td><td>0.29</td></tr>
</table>
* Large loss to follow-up with only data on 19 and 37 patients available for analysis at the study end-point and two patients unaccounted for.
† n=86 at first follow-up (6 months)
‡ n=76 at first follow-up
</td>
</tr>
<tr>
<td>(Wyler et al 2009)
Single centre, Switzerland
Accrual:
BT patients, March 2001 – December 2004
EBRT patients, January 2002 – December 2004</td>
<td>Retrospective cohort
Level III-2 interventional evidence
Downs and Black quality score: 14/27
Overall quality assessment: Poor</td>
<td>
N: 212 consecutive patients with clinically localised prostate cancer
<table>
<tr><th></th><th>LDRBT</th><th>RP</th></tr>
<tr><td>n</td><td>70</td><td>142</td></tr>
<tr><td>Age, years (range)</td><td>61 (49–75)</td><td>64 (47–75)</td></tr>
<tr><td>PSA, ng/mL</td><td>6.1 (1.1–12.8)</td><td>11.3 (0.3–24)</td></tr>
<tr><td>Gleason score</td><td>5.7 (4–7)</td><td>6.3 (5–9)</td></tr>
</table>
79% of LDRBT patients and 74% of RP patients returned questionnaires.
</td>
<td>
Symptom scale outcomes (0–100, with higher scores indicating better HRQoL)
<table>
<tr><th></th><th>5–12 months</th><th>13–24 months</th><th>37–53 months</th></tr>
<tr><td>Constipation</td><td></td><td></td><td></td></tr>
<tr><td>RP</td><td>40±43.5</td><td>12.5±17.3</td><td>11.1±19.2</td></tr>
<tr><td>LDRBT</td><td>33.3±47.1</td><td>3.3±10.5</td><td>0</td></tr>
</table>
No changes in bowel symptoms were observed within groups over time and no statistically significant difference was observed between groups.
<table>
<tr><td>Diarrhoea</td><td></td><td></td><td></td></tr>
<tr><td>RP</td><td>20±18.3</td><td>4.2±11.8*</td><td>0</td></tr>
<tr><td>LDRBT†</td><td>0</td><td>13.3±17.2*</td><td>6.7±14.9</td></tr>
</table>
* Between-group comparison (Mann-Whitney U test), p=0.009
† Within-group comparison (Kruskal-Wallis test), p=0.031
Number of patients for whom data were provided in results section is small and does not agree with reporting elsewhere in the paper that 79% and 74% of LDRBT and RP patients, respectively, returned questionnaires.
</td>
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</table>

Study	Study design and quality appraisal	Population	Bowel function
(Pinkawa et al 2009) Single centre, Germany Accrual: 2003–2006	Comparison of two matched single arms Level III-3 interventional evidence Downs and Black quality score: **16/27** Overall quality assessment: **Moderate**	**N: 104** (52 in each group). LDRBT / EBRT Age, years (range): 68 (51–77) / 68 (48–77) PSA, ng/mL: 7 (1.5–14) / 8 (2.5–24) Gleason score < 7: 50 (96) / 39 (75) Values are median (range) or n (%).	**Mean (quartiles) function and bother scores from the EPIC questionnaire†** Time A§ / Time B / Time C Bowel function: EBRT: 93 (88;96;100) / 77 (65;81;92) / 89 (82;92;96) LDRBT: 94 (92;96;100) / 81 (71;85;96) / 93 (92;96;100) Bowel bother: EBRT: 95 (93;100;100) / 76 (58;83;96) / 87 (79;96;100) LDRBT: 94 (93;100;100) / 82 (75;89;100) / 93 (93;100;100) † EPIC scale 0–100, with higher scores representing better HRQoL. No significant differences were observed between treatment groups (p=0.05). Quartiles = 25th, 50th and 75th percentiles. **Comparison of function and bother scores from the EPIC questionnaire** Time A vs B, p-value / Time A vs C, p-value Bowel function: EBRT: <0.01 / <0.05 LDRBT: <0.01 / NS Bowel bother: EBRT: <0.01 / <0.01 LDRBT: <0.01 / NS‡ § Time A = before LDRBT/EBRT, Time B = 1 month after LDRBT / on the last day of EBRT, Time C = median 16 months after LDRBT/EBRT. ‡ Not significant (p=0.05) **Selected symptoms from the EPIC questionnaire** Time A (%) / Time B (%) / Time C (%) Bloody stools ≥ rarely:

Study	Study design and quality appraisal	Population	Bowel function
			EBRT 8 14 17 LDRBT 12 12 12 Painful bowel movements ≥ rarely: EBRT 19 52* 35† LDRBT 12 27 15 Moderate/big problem from increased frequency of bowel movements: EBRT 2 33 12† LDRBT 2 18 2 * p<0.01, † p<0.05 (responses in EBRT group are significantly different than in the LDRBT group)
(Keyes et al 2009) Multicentre, Canada Accrual: July 1998 – June 2003	Case series Level IV interventional evidence NHMRC case series quality score: **5/6** Overall quality assessment: **Good**	**N=712** eligible from 932 consecutive patients Age, years Median 65.5 (46–82) Clinical stage < T2c Gleason score ≤ 7 PSA, ng/mL: ≤ 10 85.8% 10 – ≤ 15 14.2% Follow-up at least 34 months: 144 excluded due to living in remote area, 35 less than 34 months follow-up, 41 with insufficient data.	RTOG side effects of Grade 2 or greater in 9.8%.
(Zelefsky et al 2007a) Single centre, US Accrual: January 1998 – December 2004	Case series Level IV interventional evidence NHMRC case series quality score: **5/6** Overall quality assessment:	**N:562** Age Not reported Clinical stage 99.8% ≤ T2 Gleason score	NCI CTCAE bowel side effects: Late grade 2 6% Late grade 3 1%

Study	Study design and quality appraisal	Population	Bowel function
	Good	99.8% ≤ 7 PSA, ng/mL: ≤ 10 94.5% 10 – ≤ 20 5.3% > 20 0.2%	
(Kao et al 2008) Single centre, US Accrual: June 1995 – February 2005	Case series Level IV interventional evidence NHMRC case series quality score: **4/6** Overall quality assessment: **Moderate**	**N: 643** men with localised prostate cancer Age Not reported Clinical stage T1a – T2c Gleason score 98.8% of patients ≤ 7 PSA Median = 6.1 ng/mL Loss to follow-up: Patient numbers available for bowel outcomes unclear.	Freedom from grade 2 or higher rectal bleeding at 3 and 5 years was reported for 91.2% and 88.5% of patients respectively.
(Eckman et al 2010) Single centre, US Accrual: 1995 – 2007	Case series Level IV interventional evidence NHMRC case series quality score: **3/6** Overall quality assessment: **Moderate**	**N: 394** Age, years Mean 67.3 (SD±7.6) Clinical stage 99.5% < T3 Gleason score 95.7% < 8 PSA Mean 7.7 (SD±4.7) ng/mL 2.8% received adjuvant EBRT.	Bowel symptoms were uncommon following treatment, although rectal bleeding increased to a peak of 26.8% [20.4–34.3] at 18 months among men who did not report rectal bleeding at baseline. At 5 years, 17.6% [13.2–23.1] of men continued to report rectal bleeding. The median time to the resolution of rectal bleeding was 19 months [12.9–24.0]. Values are mean estimates (95% CI) from logistic regression models using generalised estimating equation methods to account for within subject correlation.
(Schafer et al 2008) Single centre, Germany Accrual: June 1998 – December 2003	Case series Level IV interventional evidence NHMRC case series quality score: **2/6** Overall quality assessment: **Poor**	**N: 258** (296 treated consecutively, 38 patients died before assessment) Age, years Median 71 Clinical stage 94% ≤ T2 Gleason score:	2.8% of men suffered 'moderate' to 'strong' faecal incontinence at a median of 51 months following implantation. 1.9% of men suffered 'moderately' to 'strongly' bloody stools at a median of 51 months following implantation.

Study	Study design and quality appraisal	Population	Bowel function
		≤ 7 71% ≥ 8 0.4% Unknown 28.6% PSA Median 7.3 ng/mL	

Table notes:
3D-CRT = three-dimensional conformal radiotherapy; ADT = androgen deprivation therapy; LDRBT = low-dose-rate brachytherapy; CTCAE = common toxicity criteria for adverse events; EBRT= external beam radiotherapy; EORTC QLQ-PR25 = European Organisation for Research and Treatment of Cancer quality of life questionnaire – prostate cancer module; EPIC = Expanded Prostate cancer Index Composite; HRQoL = health-related quality of life; IMRT = intensity modulated radiotherapy; NA = not assessed; RP = radical prostatectomy; RTOG = Radiation Therapy Oncology Group; UCLA-PCI = University of California, Los Angeles – Prostate Cancer Index

Appendix F Data tables for sexual dysfunction side effects

Table 33 Sexual dysfunction resulting from low-dose-rate brachytherapy, radical prostatectomy, external beam radiotherapy and active surveillance for the treatment of localised prostate cancer

Study	Study design and quality appraisal	Population	Sexual function
(Giberti et al 2009) Single centre, Italy Accrual: May 1999 – October 2002	Randomised controlled trial Level II interventional evidence Downs and Black quality score: **19/27** Overall quality assessment: **Moderate**	**N: 100** RP patients and **100** LDRBT patients Questionnaires were completed for 89 RP patients and 85 LDRBT patients Exclusion criteria were in accordance with American Brachytherapy Society. RP / LDRBT No. patients: 100 / 100 Age, years: 65.2 (57–74) / 65.6 (56–74) Gleason score: 5.9 / 5.7 PSA, ng/mL: 7.8 (3.5–10) / 7.5 (2.9–9.3) Values are mean (range) unless otherwise indicated.	**Mean scores from questionnaires at four time points** (higher scores indicate worse function/symptoms) Pre-treatment / 6 months / 1 year / 5 years EORTC-QLQ-PR25: Sexual function RP 5 / 9 (0.03) / 7 (NS) / 7 (NS) LDRBT 6 / 10 (0.03) / 7 (NS) / 8 (NS) Sexual activity RP 6 / 10 (0.03) / 8 (NS) / 8 (NS) LDRBT 6 / 11 (0.02) / 8 (NS) / 8 (NS) IIEF: RP 23.2 / 16.3 (0.02) / 22.2 (NS) / 22 (NS) LDRBT 22.9 / 18.5 (0.03) / 21.9 (NS) / 21.2 (NS) **Percentage of patients reporting good erectile function (mean IIEF score > 22, scale 0–25)** RP / LDRBT Pre-treatment: 62 / 60 6 months: 40 / 58 1 year: 68 / 78 5 years: 65 / 68
(Buron et al 2007) Multicentre, France Accrual:	Prospective cohort Level III-2 interventional evidence Downs and Black quality	**N: 435** men with low-risk prostate cancer from 11 French hospitals treated with LDRBT (308) or RP (127) RP / LDRBT	**Sexual outcomes, EORTC QLQ-PR25** RP / LDRBT Erectile function worse

Study	Study design and quality appraisal	Population	Sexual function
March 2001 – June 2002	score: **17/27** Overall quality assessment: **Moderate**	Age, years 62.7±6 65.2±6.3 Neoadjuvant hormones (%) 6.3 43.5 IPSS 7.8 5.9 Values are mean±standard deviation. Loss to follow-up after 24 months was between 35% and 59% (N data not provided) depending on treatment arm—see study profile for further details. Values are mean±standard deviation, unless otherwise specified.	than baseline*, %: 6 months 88 50.8 18 months 83.3 45.8 Treatment of impotence, %: 12 months 32 12.5 Note: p-values not provided; main in-text data summarised as no other exact values could be determined from the graphical presentation of results. * Among sexually active men Neo-adjuvant hormonal therapy among RP patients was 6.3% compared with 43.5% among LDRBT patients.
(Ferrer et al 2008) Multicentre, Spain Accrual: April 2003 – March 2005	Prospective cohort Level III-2 interventional evidence Downs and Black quality score: **17/27** Overall quality assessment: **Moderate**	**N: 841** organ-confined prostate cancer patients RP EBRT LDRBT Age, years 64±5.5 69.2±5.5 66.9±6.5 PSA, ng/mL 7.9±3.3 10.1±7.9 6.9±2.3 Gleason score 6.8±6.2 6±1.1 5.7±4.4 Values are mean±standard deviation. Loss to follow-up: 614 patients treated with LDRBT (275), RP (134) and EBRT (205) were included in HRQoL analysis.	**Mean HRQoL scores at 2-year follow-up for low-risk patients by treatment group** RP EBRT LDRBT EPIC* sexual 33±21.6 42.2±22.5 50.5±23.9 **p-values for one-way comparison of HRQoL scores** RP vs EBRT RP vs LDRBT LDRBT vs EBRT EPIC sexual <0.001 <0.001 <0.001 * All EPIC items were answered on a 5-point Likert scale and transformed linearly to a scale of 0 to 100, with higher scores indicating better HRQoL.
(Hashine et al 2008) Single centre, Japan Accrual: January 2003 – July 2005	Prospective cohort Level III-2 interventional evidence Downs and Black quality score: **17/27** Overall quality assessment: **Moderate**	**N: 213** (131 RP and 82 LDRBT patients) RP LDRBT p-value Age, years* (range) 68.0 (42–78) 70.5 (50–85) 0.016 PSA, ng/mL* 9.6 6.7 <0.001 Gleason score, n: <0.001 5–6 44 51	**UCLA-PCI scores** (mean±SD)* RP LDRBT p-value† Sexual function: Baseline 43.4±25.1 32.4±29.1 0.416 1 month 2.7±8.1 29.6±25.4 <0.001 3 months 2.5±6.7 29.7±24.6 <0.001 6 months 3.6±8.2 35.3±26.7 <0.001 12 months 5.2±11.0 26.4±24.4 <0.001

Study	Study design and quality appraisal	Population	Sexual function
		7 42 27 8–10 36 4 Neoadjuvant hormones 8 18 0.002 Nerve-sparing 22 - EBRT - 1 *Median	Sexual bother: Baseline 67.6±31.3 75.4±26.3 0.146 1 month 59.6±37.4 78.3±27.8 0.005 3 months 58.2±36.4 69.6±28.0 0.111 6 months 53.8±35.8 76.7±27.5 0.002 12 months 51.6±35.0 73.8±31.9 <0.001 * All UCLA-PCI scores were transformed to a scale of 0 –100, with higher scores representing better HRQoL † Mann-Whitney U test
(Smith et al 2010) Population-based, NSW, Australia Accrual: October 2000 – May 2003	Prospective cohort Level III-2 interventional evidence Downs and Black quality score: **17/27** Overall quality assessment: **Moderate**	**N: 4542** men (3,195 with histologically confirmed T1a–2c prostate cancer and 1,347 controls with no diagnosis of prostate cancer, as indicated and cross-checked against registry data) All potential participants had to be physically and mentally capable of a 30-minute telephone interview in English Cases, n Controls, n Potentially eligible 3,195 1,347 Final analysis 1,636 495 AS 200 NA RP 981 NA EBRT 123 NA Combined EBRT/ADT 166 NA LDRBT 58 NA Mean age, years [95% CI] 61.2 [60.7, 61.7] 61.2 [61, 61.5] Note: Patients who received high-dose-rate BT and ADT alone were also assessed in the study, but were not considered for the purposes of this review.	**Unadjusted mean sexual function** (score range 0–100; higher scores indicate better function), mean±SD Baseline 3 years AS 61.0±24.8 44.1±29 Nerve-sparing RP 71.8±21.7 34.7±27.7 Non-nerve-sparing RP 63.3±26.8 22±23.6 EBRT 57.4±28.0 32.0±29.0 Combined EBRT/ADT 50.6±28.6 22.1±25.9 LDRBT 69.8±25.2 54.0±25.7 Controls 66.0±25.7 57.1 **Unadjusted mean sexual bother** (score range 0–100; higher scores indicate better function), mean±SD Baseline 3 years AS 67.0±37.2 65.9±37.9 Nerve-sparing RP 78.9±32.0 52.2±39.7 Non-nerve-sparing RP 71.1±36.5 53.6±42.2 EBRT 74.6±33.5 57.6±41.9

Study	Study design and quality appraisal	Population	Sexual function
			Combined EBRT/ADT 65.1±37.9 58.4±42.2 LDRBT 81.9±29.5 66.8±32.7 Controls 75.3±34.0 78.5 **Impotence, n (%)** Baseline 3 years AS 53 (27.3) 94 (54.3) RP 206 (21.5) 695 (77.4) EBRT 35 (30.2) 72 (67.9) Combined EBRT/ADT 63 (39.1) 121 (82.3) LDRBT 11 (19.0) 20 (36.4) Controls 109 (23.3) NA† † Controls were not asked the relevant questions at year 3.
(Frank et al 2007) Radiation oncology department, US Accrual: 1998–2000	Retrospective cohort Level III-2 interventional evidence Downs and Black quality score: **16/27** Overall quality assessment: **Moderate**	**N: 960** men treated with LDRBT (160), RP (400) and HDR EBRT (400) LDRBT RP EBRT Age, years 64 61 68 Values are median. Loss to follow-up: 625/960 (65%) in total completed a survey, of whom 443 were found to have undergone monotherapy and were included in the analysis—see study profile for further details.	**EPIC domain specific prostate cancer HRQoL scores†** (mean±SD) [95% CI] LDRBT EBRT RP Sexual function 37.8±27.2 [31.5,44.1] 28±27.9 [23.3,32.8] 25.1±24.5 [21.9,28.2] Sexual bother 49.4±31.9 [42,56.8] 50.2±36.7 [43.9,56.4] 44.7±31.8 [40.6,48.8] LDRBT patients had significantly better sexual function than patients treated with EBRT (p<0.01) and RP (p<0.001). No difference in sexual bother was observed among the three treatment modalities (p=0.35). † Higher scores indicate better HRQoL outcomes (scale 0–100).
(Guedea et al 2009) Single centre, Spain April 2003 – March 2005	Prospective cohort Level III-2 interventional evidence Downs and Black quality score: **16/27**	**N: 304** men with prostate cancer LDRBT RP EBRT n 56 114 143	**Baseline EPIC scores*** RP EBRT LDRBT Sexual summary 58.3±24 50.3±24.6 54.0±25.4

Study	Study design and quality appraisal	Population	Sexual function
	Overall quality assessment: **Moderate**	Age, years 67.5 63.9 68.8 PSA, ng/mL 6.4 7.9 11.9 Gleason score 5.7 6.3 6.4 Values are mean and n as indicated.	**Comparison of EPIC scores at baseline** Sexual summary, p-value RP vs LDRBT NS‡ RP vs EBRT 0.041§ EBRT vs LDRBT NS Overall <0.001† ‡ Not significant § Tukey's studentised comparison **Change in EPIC score at 2 years post treatment** RP EBRT LDRBT EPIC Sexual summary –26.6±27.4 –6.9±27.3 –6.3±27.3 **Comparison of EPIC scores after 2 years** Sexual summary, p-value RP vs LDRBT <0.05 RP vs EBRT <0.05 EBRT vs LDRBT NR** Overall <0.001† ** Not reported † ANOVA **Change of EPIC score at 2 years post treatment, multivariate generalised estimating equation (GEE) model#** RP EBRT LDRBT EPIC

Study	Study design and quality appraisal	Population	Sexual function
			Sexual summary –18.74±4.46 –3.39±4.44 (reference) **Comparison of treatment scores after 2 years, GEE model** Sexual summary, p-value LDRBT vs RP <0.001# RP vs EBRT NR EBRT vs LDRBT NR # Adjusting for age, baseline scores, risk group and hormonal treatment, at 2 years post treatment * EPIC scores in range 0–100, with higher scores indicating better HRQoL Values are mean±SD unless otherwise indicated.
(Wei et al 2002) Single centre, US Accrual: June 1995 – May 1999	Retrospective cohort Level III-2 interventional evidence Downs and Black quality score: **16/27** Overall quality assessment: **Moderate**	**N: 1,014** including 142 male controls who are not further considered‡ LDRBT n 114 Age, years 67.2±7.3 Time since primary therapy, months 21 Adjuvant/ neoadjuvant therapy, % 51 PSA, ng/mL 9.7±14.9 Gleason score, %: 2–6 68.3 7 23.2 8–10 8.5 EBRT RP n 203 896	**EPIC* sexual summary scores for follow-up exceeding 1 year** Sexual LDRBT EBRT RP 26.9† [18.2,35.6] 38.8† [32.3,45.3] 33.9 [29.6,38.1] * Expanded Prostate Cancer Index, values are mean [99% CI]. Multivariable modelling was used to adjust for age, time since therapy, Gleason score, clinical stage, PSA and use of hormonal therapy. † Values that share a common symbol were significantly different in a pairwise comparison (significance set at 0.008 after Tukey adjustment for comparisons between three groups), p<0.007.

Study	Study design and quality appraisal	Population			Sexual function			
		Age, years	70.9±7.2	63.5±7.8				
		Time since primary therapy, months	29	30				
		Adjuvant/ neoadjuvant therapy, %	33	28				
		PSA, ng/mL	9.1±12.7	7.3±7.2				
		Gleason score, %:						
		2–6	43.1	59.6				
		7	47.9	37.3				
		8–10	9.0	3.1				
		Values are median±SD, except where indicated.						
		‡ A control group of healthy males was unnecessary for data extraction and irrelevant to the research questions of this review.						
(Tsui et al 2005) Single institution, Canada Accrual: 1998–2000	Retrospective cohort Level III-2 interventional evidence Downs and Black quality score: **15/27** Overall quality assessment: **Poor**	**N: 202**			**Potency with and without sildenafil use***			
			LDRBT	RT		LDRBT†	EBRT‡	p-value
		N	86	76	Patients potent without sildenafil use, %:			
		Age, years			6 months	69.2	53.3	0.34
		Mean±SD	64.8±6.5	66.3±5.1	12 months	73.9	56.3	0.31
		PSA (ng/mL)			18 months	76.2	42.1	0.052
		Mean±SD	6.2 (2.3)	9.1 (3.7)	24 months	79.2	69.2	0.69
		Gleason score, n (%):†			30 months	84.2	72.7	0.64
		≤ 6	83 (97.6)	30 (40.5)	36 months	70	77.8	1.0
		7	2 (2.4)	41 (55.4)	42 months	90	100	1.0
		8	0 (0)	3 (4.1)	Patients potent with sildenafil use, %:			
		α-blocker, %	3.5	6.6	6 months	88.5	75	0.39
		Neoadjuvant ADT, %	32.9	13.2*	12 months	95.7	68.8	0.033
					18 months	90.9	47.4	0.005
					24 months	100	84.6	0.12
					30 months	100	81.8	0.13

Study	Study design and quality appraisal	Population	Sexual function
		Values are mean±SD unless otherwise specified. † p<0.001, * p=0.005	36 months 90 100 1.0 42 months 100 100 1.0 * Prevalence of PDE5 inhibitor use was not reported, and authors admit that LDRBT patients were often encouraged to use PDE5 inhibitors whereas EBRT patients were seldom offered PDE5 inhibitors. Large loss to follow-up with data on only 10 and 7 patients for the LDRBT and EBRT groups, respectively, available for analysis at the study end-point and two patients unaccounted for. † n=35 at first follow-up (6 months) ‡ n=32 at first follow-up
(Pinkawa et al 2009) Single centre, Germany Accrual: 2003–2006	Comparison of two matched single arms Level III-3 interventional evidence Downs and Black quality score: **16/27** Overall quality assessment: **Moderate**	**N: 104** (52 in each group) LDRBT EBRT Age, years 68 (51–77) 68 (48–77) PSA, ng/mL 7 (1.5–14) 8 (2.5–24) Gleason score < 7, n (%) 50 (96) 39 (75) Neoadjuvant hormones, n (%) 14 (27) 14 (27) Values are median (range) unless otherwise specified.	**Mean (quartiles) function and bother scores from the EPIC questionnaire†** Time A§ Time B Time C Sexual function: EBRT 43 (29;44;56) 32 (17;30;50) 37 (12;32;59) LDRBT 46 (32;50;62) 36 (17;37;60) 42 (25;41;59) Sexual bother: EBRT 67 (44;81;100) 54 (25;50;88) 60 (31;69;94) LDRBT 72 (50;75;100) 58 (30;53;83) 61 (31;63;88) § Time A = before LDRBT/EBRT, Time B = 1 month after LDRBT / on the last day of EBRT, Time C = median 16 months after LDRBT/EBRT No statistically significant differences were observed between treatment groups, p=0.05. Quartiles = 25th, 50th and 75th percentiles. **Comparison of function and bother scores from the EPIC questionnaire** Time A vs B, p-value Time A vs C, p-value Sexual function: EBRT <0.01 <0.01

Study	Study design and quality appraisal	Population	Sexual function
			LDRBT <0.01 <0.01 Sexual bother: EBRT <0.01 <0.01 LDRBT <0.01 <0.05 **Other sexual outcomes** LDRBT EBRT Patients with erectile ability before treatment, n 44 42 Patients with erectile ability post-treatment #, % 81 84 Patients with erections sufficient for sex before treatment, n 29 31 Patients with erections sufficient for sex post-treatment ‡, % 67 51 † EPIC scale 0–100, with higher scores representing better HRQoL # among patients with erectile ability before treatment ‡ among patients with erections sufficient for sex before treatment
(Keyes et al 2009) Multicentre, Canada Accrual: July 1998 – June 2003	Case series Level IV interventional evidence NHMRC case series quality score: **5/6** Overall quality assessment: **Good**	**N: 712** eligible from 932 consecutive patients Age, years Median 65.5 (46–82) Clinical stage < T2c Gleason score ≤ 7 PSA ≤ 10 ng/mL 85.8% 10 – ≤ 15 ng/mL 14.2% Follow-up at least 34 months: 144 excluded due to living in remote area, 35 less than 34 months follow-up, 41 with insufficient data.	Erectile function at least 12 months following LDRBT in men with known baseline erectile function (n=706) had remained unchanged or improved for 59.5% and had worsened in 40.5%.

Study	Study design and quality appraisal	Population	Sexual function
(Kao et al 2008) Single centre, US Accrual: June 1995 – February 2005	Case series Level IV interventional evidence NHMRC case series quality score: **4/6** Overall quality assessment: **Moderate**	**N: 643** Age Not reported Clinical stage T1a–T2c Gleason score 98.8% of patients ≤ 7 PSA Median = 6.1 ng/mL Loss to follow-up: Erectile function data were available for 572 men, of whom 420 were potent and assessed following treatment.	Potency was preserved in 86.8% and 73.4% patients after 3 and 5 years respectively.
(MacDonald et al 2005) Single centre, Canada Accrual: July 1998 – January 2002	Case series Level IV interventional evidence NHMRC case series quality score: **4/6** Overall quality assessment: **Moderate**	**N: 342 men potent at baseline** Age, years Median 65 (49–80) Clinical stage ≤ T2 Gleason score ≤ 7 PSA, ng/mL Mean 6.7 (SD±3.3) Prostate volume < 50 cc	Physician-documented / Patient-documented ED at 1 year (%): 57 / 70 ED at 2 years (%): 48 / 66 ED at 3 years (%): 38 / NR Response rates for patient documented sexual function dropped to 52% at year 2. Physician-documented sexual function was for 98%, 99% and 58% of patients at year 1, 2 and 3 respectively.
(Eckman et al 2010) Single centre, US Accrual: 1995–2007	Case series Level IV interventional evidence NHMRC case series quality score: **3/6** Overall quality assessment: **Moderate**	**N: 394** Age, years Mean 67.3 (SD±7.6) Clinical stage 99.5% < T3 Gleason score 95.7% < 8 PSA, ng/mL Mean 7.7 (SD±4.7) 2.8% received adjuvant EBRT.	Month 3, % [95% CI] / Median time to resolution, months [95% CI] Impaired potency: 25.4 [17.6, 35.1] / 45 [23–60] Blood in semen: 11.9 [4.9, 26.2} / not reported Painful ejaculation: 23.1 [10.5, 43.4] / not reported Medication for ED: 2.8 [1.8, 4.4] / not reported Values are mean estimates (95% CI) from logistic regression models using generalised estimating equation methods to account for within subject correlation—estimates are of men who did not report the particular symptom

Study	Study design and quality appraisal	Population	Sexual function
			at baseline. Impaired potency continued to increase following treatment and was reported in 42.6% [33.4, 52.4] of men at 5 years. The use of medication also continued to increase and reached 21.5% [17.2, 26.4] by 5 years.

Table notes:
3D-CRT = three-dimensional conformal radiotherapy; ADT = androgen deprivation therapy; LDRBT = low-dose-rate brachytherapy; EBRT = external beam radiotherapy; EORTC QLQ-PR25 = European Organisation for Research and Treatment of Cancer quality of life questionnaire – prostate cancer module; EPIC = Expanded Prostate cancer Index Composite; HRQoL = health-related quality of life; IIEF = International Index of Erectile Function; IMRT = intensity modulated radiotherapy; NR = not reported; RP = radical prostatectomy; UCLA-PCI = University of California, Los Angeles – Prostate Cancer Index

Appendix G Data tables for health-related quality of life

Table 34 Effects on health-related quality of life resulting from low-dose-rate brachytherapy, radical prostatectomy, external beam radiotherapy and active surveillance for the treatment of localised prostate cancer

Study	Study design and quality appraisal	Population	General health-related quality of life
(Giberti et al 2009) Single centre, Italy Accrual: May 1999 – October 2002	Randomised controlled trial Level II interventional evidence Downs and Black quality score: **19/27** Overall quality assessment: **Moderate**	**N: 100** RP patients and **100** LDRBT patients Questionnaires were completed for 89 RP patients and 85 LDRBT patients. Exclusion criteria were in accordance with American Brachytherapy Society. RP / LDRBT No. patients: 100 / 100 Age, years: 65.2 (57–74) / 65.6 (56–74) Gleason score: 5.9 / 5.7 PSA, ng/mL: 7.8 (3.5–10) / 7.5 (2.9–9.3) Values are mean (range) unless otherwise indicated.	**Mean scores from questionnaires at four time points** (higher scores indicate worse function/symptoms) Pre-treatment / 6 months / 1 year / 5 years EORTC-QLQ Physical function: RP 91 / 86 (0.02) / 86 (0.02) / 90 (NS) LDRBT 94 / 90 (0.03) / 90 (0.03) / 94 (NS) Role function: RP 93 / 87 (0.01) / 90 (NS) / 90 (NS) LDRBT 95 / 90 (0.02) / 93 (NS) / 94 (NS) Emotional function: RP 82 / 87 (0.02) / 86 (0.03) / 84 (NS) LDRBT 80 / 86 (0.01) / 84 (0.03) / 82 (NS) Cognitive function: RP 91 / 88 (0.04) / 90 (NS) / 90 (NS) LDRBT 87 / 88 (NS) / 88 (NS) / 88 (NS) Social function: RP 89 / 84 (0.02) / 89 (NS) / 89 (NS) LDRBT 92 / 87 (0.02) / 93 (NS) / 94 (NS) Global health: RP 79 / 74 (0.02) / 78 (NS) / 78 (NS) LDRBT 83 / 79 (0.03) / 81 (NS) / 82 (NS) Fatigue: RP 16 / 20 (0.03) / 18 (NS) / 18 (NS) LDRBT 17 / 22 (0.02) / 19 (NS) / 18 (NS) Nausea/vomiting:

Study	Study design and quality appraisal	Population	General health-related quality of life
			RP 0 1 (NS) 1 (NS) 1 (NS) LDRBT 0 2 (NS) 2 (NS) 1 (NS) Pain: RP 8 12 (0.02) 9 (NS) 9 (NS) LDRBT 5 15 (<0.01) 8 (NS) 8 (NS) Dyspnoea: RP 8 8 (NS) 8 (NS) 8 (NS) LDRBT 9 11 (NS) 10 (NS) 11 (NS) Insomnia: RP 21 24 (0.04) 23 (NS) 22 (NS) LDRBT 20 21 (NS) 20 (NS) 20 (NS) Appetite loss: RP 3 4 (NS) 4 (NS) 3 (NS) LDRBT 5 4 (NS) 4 (NS) 4 (NS)
(Lee et al 2001) Single institution, US Accrual: May 1998 – June 1999	Prospective cohort Level III-2 interventional evidence Downs and Black quality score: **22/27** Overall quality assessment: **Moderate**	**N: 90** All patients treated between May 1998 and June 1999 (n=98) were offered enrolment. 90 patients (91%) agreed to complete the FACT-P and IPSS questionnaire. LDRBT N 44 Age, years 67.1 (49–79) Stage, n (%) T1 26 (59) T2 18 (41) PSA, ng/mL 6.5 (1.3–13.5) Gleason score n (%): ≤ 6 38 (86)† 7 6 (14) > 7 0 (0) EBRT	FACT-P scores at baseline, 1, 3 and 12 months following treatment T0 T1 T3 T12 LDRBT 138.4 (±17.0) 120.5 (±21.7) 130.0 (±18.4) 138.5 (±14.2) EBRT 137.1 (±12.1) 129.5 (±21.0) 134.4 (±19.2) 136.9 (±15.6) RP 138.3 (±14.7) 117.7 (±18.3) 134.4 (±17.8) 140.4 (±14.9) By 12 months following treatment, there were no differences in mean FACT-P score in any treatment group compared to baseline. Men treated with LDRBT and RP experienced a greater decline in FACT-P in the first month than men treated with EBRT (p=0.0288 and 0.0132 respectively). There was no statistical difference in FACT-P between the RP and LDRBT groups. Adjusting for baseline FACT-P score, age, race, clinical stage, pre-treatment hormonal therapy and Gleason score, treatment remained a significant predictor of FACT-P score at 1 month (p=0.0434).

Study	Study design and quality appraisal	Population	General health-related quality of life
		N 23 Age, years 68.8 (51–79) Stage, n (%) T1 12 (52) T2 11 (48) PSA, ng/mL 8.1 (2.9–19.6) Gleason score n (%): ≤ 6 11 (48) 7 10 (43) > 7 2 (9) RP N 23 Age, years 61.0 (42–68)* Stage, n (%) T1 19 (83) T2 4 (17) PSA, ng/mL 6.2 (1.3–12.0) Gleason score n (%): ≤ 6 16 (69) 7 5 (22) > 7 2 (9) Values are median (range) or n (%). † significantly more Gleason ≤ 6 than RP or EBRT (p=0.015), * significantly younger than LDRBT or EBRT (p=0.0006).	
(Buron et al 2007) Multicentre, France Accrual: March 2001 – June 2002	Prospective cohort Level III-2 interventional evidence Downs and Black quality score: **17/27** Overall quality assessment:	**N: 435** men with low-risk prostate cancer from 11 French hospitals treated with LDRBT (308) or RP (127) RP LDRBT Age, years 62.7±6 65.2±6.3 Neoadjuvant	**Intragroup QLQ-C30 score changes over time#** $Mean_{RP}$ (p-value*) $Mean_{BT}$ (p-value*) T0–TE† Global health –18.0 (<0.0001) –5.8 (<0.0001) Physical functioning –28.7 (<0.0001) –2.8 (<0.0001) Role functioning –48.3 (<0.0001) –7.2 (<0.0001)

Study	Study design and quality appraisal	Population	General health-related quality of life
	Moderate	hormones (%) 6.3 43.5 IPSS 7.8 5.9 Values are mean±standard deviation Loss to follow-up after 24 months was between 35% and 59% (N data not provided) depending on treatment arm—see study profile for further details. Values are mean±SD, unless otherwise specified.	Emotional functioning –6.4 (0.0139) 2.8 (0.0082) Cognitive functioning –7.6 (0.0019) 1.0 (0.189) Social functioning –40.5 (<0.0001) –7.3 (<0.0001) Fatigue 38.1 (<0.0001) 7.1 (<0.0001) Pain 28.9 (<0.0001) 6.0 (<0.0001) Dyspnoea 8.5 (0.0022) –0.1 (0.9031) Insomnia 15.0 (0.0004) 0.8 (0.6052) Appetite loss 20.9 (<0.0001) 2.6 (0.0073) Constipation 15.0 (<0.0001) 3.8 (0.0009) T0–T2 Global health –2.9 (0.180) –6.8 (<0.0001) Physical functioning –6.3 (0.0001) –2.2 (0.0006) Role functioning –16.8 (<0.0001) –5.9 (<0.0001) Social functioning –13.3 (<0.0001) –8.8 (<0.0001) Fatigue 9.8 (0.0001) 6.7 (<0.0001) Pain 2.2 (0.3793) 6.9 (<0.0001) Diarrhoea 2.2 (0.1812) 4.8 (0.0002) T0–T6 Global health 1.8 (0.3863) –3.6 (0.0044) Emotional functioning 6.4 (0.0034) 8.9 (<0.0001) T0–T12 Global health 4.3 (0.1063) –0.6 (0.6052) Emotional functioning 8.5 (0.0034) 7.0 (<0.0001) T0–T18 Global health 6.9 (0.0274) –0.6 (0.6052) Emotional functioning 10.6 (0.0028) 6.9 (<0.0001) Appetite loss –5.7 (0.0585) 0.8 (0.3953) T0–T24 Global health 7.7 (0.0101) 0.8 (0.5223) Emotional functioning 12.1 (0.0003) 9.3 (<0.0001) * 90 pairwise comparisons were made for intragroup changes and p<0.0006 (0.05/90) was considered as significant. † T0 = before treatment, TE = immediately after treatment, Tn = n months after treatment

Study	Study design and quality appraisal	Population	General health-related quality of life

Intergroup QLQ-C30# score changes over time

	$Mean_{BT/RP}$	95% CI	p-value‡
T0–TE			
Global health	13.5	[7.5,19.6]	<0.0001
Physical functioning	25.9	[20.9,30.9]	<0.0001
Role functioning	39.9	[30.7,49.1]	<0.0001
Emotional functioning	9.8	[3.5,16.1]	0.0008
Cognitive functioning	9.2	[4.0,14.4]	0.0001
Social functioning	32.7	[24.4,40.9]	<0.0001
Fatigue	–31.2	[–38.3, –24.0]	<0.0001
Pain	–21.7	[–29.4, –14.1]	<0.0001
Dyspnoea	–8.5	[–15.0,2.0]	0.0065
Insomnia	–15.7	[–25, –6.4]	0.0002
Appetite loss	–19.1	[–25.5, –12.7]	<0.0001
Constipation	–12.5	[–19.8, –5.3]	0.0002
T0–T2			
Global health	–4.0	[–10.0,3.0]	0.2720
Physical functioning	–3.5	[–0.3,7.2]	0.0812
Role functioning	11.1	[3.7,18.5]	0.0014
Social functioning	4.4	[–2.7,11.6]	0.3128
Fatigue	–1.0	[–7.7,5.8]	0.9376
Pain	5.7	[–1.3,12.7]	0.1340
Diarrhoea	3.3	[–3.2,9.8]	0.4588
T0–T6			
Global health	–7.5	[–13.9, –1.1]	0.0164
Emotional functioning	3.6	[–3.5,10.5]	0.4698
T0–T12			
Global health	–7.9	[–14.8, –1.0]	0.0195
Emotional functioning	–1.3	[–8.9,6.2]	0.9087
T0–T18			
Global health	–8.3	[–16, –0.4]	0.0377
Emotional functioning	–5.6	[–10.9,5.6]	0.7312
Appetite loss	7.9	[1.7,14.2]	0.0083
T0–T24			
Global health	–8.2	[–16.0, –0.4]	0.0379

Study	Study design and quality appraisal	Population	General health-related quality of life
			Emotional functioning –2.7 [–11.4,6.0] 0.7422 ‡ Analysis of covariance (ANCOVA) for difference in QLQ-C30 changes relative to baseline after adjusting for age, working status, PSA, Gleason score, use of neoadjuvant hormonal therapy and pre-treatment IPSS (International Prostate Symptom Score). \# EORTC-QLQ-30 is scored on a scale of 0–100, with higher scores representing better HRQoL.
(Ferrer et al 2008) Multicentre, Spain Accrual: April 2003 – March 2005	Prospective cohort Level III-2 interventional evidence Downs and Black quality score: **17/27** Overall quality assessment: **Moderate**	**N: 841** organ-confined prostate cancer patients RP EBRT LDRBT Age, years 64±5.5 69.2±5.5 66.9±6.5 PSA, ng/mL 7.9±3.3 10.1±7.9 6.9±2.3 Gleason score 6.8±6.2 6±1.1 5.7±4.4 Values are mean±standard deviation Loss to follow-up: 614 patients treated with LDRBT (275), RP (134) and EBRT (205) were included in HRQoL analysis.	**Quality of life measures for men treated with LDRBT** (mean±SE; higher scores represent better health/function)* Pre-treatment 3 months 12 months 24 months SF-36 PCS 54±0.5 53.1±0.3 (0.07)† 52.4±0.4 (<0.001) 50.9±0.5 (<0.001) SF-36 MCS 54.3±0.4 54.7±0.5 (1.0) 56.5±0.4 (<0.001) 56.3±0.4 (0.002) FACT-G 80.4±0.6 81±0.6 (1.0) 82.5±0.6 0.018 79.8±0.6 1.0 FACT-P 39.4±0.3 38.1±0.3 <0.001 39.5±0.3 1.0 38.9±0.3 0.663 * 6 months' follow-up data were reported but excluded from this analysis as there were no significant differences from baseline at 6 months. **Quality of life measures for men treated with RP** (mean±SE)‡ Pre-treatment 3 months 6 months 24 months SF-36 PCS 54±0.5 51.9±0.5 0.001 53±0.5 0.986 50.6±0.8 <0.001 SF-36 MCS 53.3±0.6 53±0.8 1.0 53.3±0.9 1.0 54.9±0.8 0.331

Study	Study design and quality appraisal	Population	General health-related quality of life
			FACT-G 79.7±0.8 78±1 78.9±1 76.6±1.1 NR NR NR FACT-P 39.8±0.4 35.6±0.5 37.9±0.4 37.2±0.5 <0.001 <0.001 <0.001 ‡ 12 months' follow-up data were reported but excluded from this analysis as there were no significant differences from baseline at 12 months. **Quality of life measures for men treated with EBRT** (mean±SE) Pre-treatment 3 months 12 months 24 months SF-36 PCS 52.5±0.5 51.4±0.5 50.9±0.5 49.2±0.6 0.089 0.007 <0.001 SF-36 MCS 54.9±0.5 55.3±0.6 56.3±0.5 56.3±0.5 1.0 0.039 0.08 FACT-G 80±0.8 80.2±0.9 80.6±0.9 77.5±0.9 1.0 1.0 0.007 FACT-P 38.9±0.4 38.1±0.4 38.7±0.4 37.5±0.4 0.225 1.0 0.001 † p-values for change from pre-treatment value (using Bonferroni adjustment for multiple comparisons). PCS = physical component summary MCS = mental component summary NR = not reported
(Hashine et al 2008) Single centre, Japan Accrual: January 2003 – July 2005	Prospective cohort Level III-2 interventional evidence Downs and Black quality score: **17/27**	**N: 213** (131 RP and 82 LDRBT patients) RP LDRBT p-value Age, years* (range) 68.0 (42–78) 70.5 (50–85) 0.016	**HRQoL at 1 month, SF-36 score*** RP LDRBT p-value† Physical functioning 84.8±12.8 87.6±17.4 0.008 Role functioning 66.2±27.4 81.4±22.9 <0.001 Body pain 71.7±22.5 79.4±23.7 0.022

Study	Study design and quality appraisal	Population	General health-related quality of life
	Overall quality assessment: **Moderate**	PSA, ng/mL* 9.6 6.7 <0.001 Gleason score, n: <0.001 5–6 44 51 7 42 27 8–10 36 4 Neoadjuvant hormones 8 18 0.002 Nerve sparing 22 - EBRT - 1 * Median	General health 63.6±15.6 62.7±17.4 0.862 Vitality 58.8±20.7 69.2±19.5 0.006 Social functioning 70.1±27.5 86.1±20.4 <0.001 Role emotional 64.1±29.3 83.5±23.7 <0.001 Mental health 61.9±21.7 72.3±18.2 0.004‡ * Mean score and SD for each of the eight SF-36 components is reported at each time point but no differences in SF-36 scores extend to 12 months; scores range 0–100, with higher scores indicating better function/health. ‡ Mental health component for RP was significantly worse at baseline; therefore, it is not clear what the impact of RP is on mental health compared with LDRBT. † Mann-Whitney U test
(Smith et al 2010) Population-based, NSW, Australia Accrual: October 2000 – May 2003	Prospective cohort Level III-2 interventional evidence Downs and Black quality score: **17/27** Overall quality assessment: **Moderate**	**N: 4,542** men (3,195 with histologically confirmed T1a–2c prostate cancer and 1,347 controls with no diagnosis of prostate cancer, as indicated and cross-checked by registry data) All potential participants had to be physically and mentally capable of a 30-minute telephone interview in English. Cases, n / Controls, n Potentially eligible 3,195 1,347 Final analysis 1,636 495 AS 200 NA RP 981 NA EBRT 123 NA Combined EBRT/ADT 166 NA LDRBT 58 NA Mean age, years [95% CI] 61.2 [60.7, 61.7] 61.2 [61, 61.5]	**Unadjusted mean physical function score** (score range 0–100; higher scores indicate better function) Baseline / 3 years AS 47.7±10.8 46.9±11.9 Nerve-sparing RP 52.3±7.6 50.1±9.0 Non-nerve-sparing RP 50.6±8.7 48.7±9.5 EBRT 49.3±9.9 46.5±10 Combined EBRT/ADT 46.7±11.3 44.1±11.7 LDRBT 52.6±7.9 49±9.6 Controls 49.4±9.6 47.9 **Unadjusted mean mental function score** (score range 0–100; higher scores indicate better function) Baseline / 3 years AS 51.4±9.5 53.1±9.2 Nerve-sparing

Study	Study design and quality appraisal	Population	General health-related quality of life
			RP 53.6±7.7 53.3±8.5 Non-nerve-sparing RP 54.4±7.4 53.7±8.5 EBRT 53.1±9 52.9±9.1 Combined EBRT/ADT 53.5±8.6 52.8±9.7 LDRBT 51.7±9.9 54±7.8 Controls 52.5±9.1 54.1
(Guedea et al 2009) Single centre, Spain April 2003 – March 2005	Prospective cohort Level III-2 interventional evidence Downs and Black quality score: **16/27** Overall quality assessment: **Moderate**	**N: 304** men with prostate cancer LDRBT RP EBRT n 56 114 143 Age, years 67.5 63.9 68.8 PSA, ng/mL 6.4 7.9 11.9 Gleason score 5.7 6.3 6.4 Values are mean and n as indicated.	**Baseline SF-36 scores‡** RP EBRT LDRBT PCS* 53.3±6 52.6±6.1 53.5±5.2 MCS† 53.7±6.2 54.1±6.2 53.7±6.9 **Change of SF-36 score at 2 years post treatment** RP EBRT LDRBT PCS –3.6±7.8 –3.3±7.1 –2.7±8.6 MCS 1.1±7.3 1.4±6.8 0.1±10.7 ‡ Range 0 –100; higher scores represent better function/health. * Physical component score † Mental component score Values are mean±SD unless otherwise indicated
(Wei et al 2002) Single centre, US Accrual: June 1995 – May 1999	Retrospective cohort Level III-2 interventional evidence Downs and Black quality score: **16/27** Overall quality assessment: **Moderate**	**N: 1,014** including 142 male controls who are not further considered‡ LDRBT n 112 Age, years 67.2±7.3 Time since primary therapy,	**FACT-P scores* for follow-up exceeding one year** LDRBT EBRT RP 32.4†# [30.1,34.8] 36.4† [34.7,38.2] 36.9# [35.8,38.2] * Functional Assessment of Cancer Therapy (prostate component), values

Study	Study design and quality appraisal	Population	General health-related quality of life
		months 21 Adjuvant/ neoadjuvant therapy, % 51 PSA, ng/mL 9.7±14.9 Gleason score, %: 2–6 68.3 7 23.2 8–10 8.5 EBRT RP n 203 896 Age, years 70.9±7.2 63.5±7.8 Time since primary therapy, months 29 30 Adjuvant/ neoadjuvant therapy, % 33 28 PSA, ng/mL 9.1±12.7 7.3±7.2 Gleason score, %: 2–6 43.1 59.6 7 47.9 37.3 8–10 9.0 3.1 Values are median±SD, except where indicated. ‡ A control group used in the primary analysis were not considered given that a secondary analysis made direct comparison between treatment modalities, in accordance with inclusion criteria for this assessment.	are mean [99% CI]. Multivariable modelling was used to adjust for age, time since therapy, Gleason score, clinical stage, PSA and use of hormonal therapy. † # Values that share a common symbol were significantly different in a pairwise comparison (significance set at 0.008 after Tukey adjustment for comparisons between three groups), p<0.0005.
(Kirschner-Hermanns et al 2008)	Prospective cohort Level III-2 interventional	**N: 94** (33 LDRBT, 61 RP patients)	**HRQoL after 1 year, EORTC-QLQ-30** (scale 0–100; higher scores indicate better health/functioning)

Study	Study design and quality appraisal	Population	General health-related quality of life
Single institution, Germany Accrual: January 1999 – December 2002	evidence Downs and Black quality score: **15/27** Overall quality assessment: **Poor**	RP Age, years† 64 (54–75) PSA, ng/mL† 9.2 (1.6–55.6) Gleason score† 5 (3–8) OCO* 0.78 (0.08–2.67) Max flow < 10 mL/s, % 30 Residual vol > 50 mL, % 34# Max capacity < 200 mL, % 15 LDRBT Age, years† 67 (57–75) PSA, ng/mL† 7.7 (3.2–17.0) Gleason score† 5 (2–7) OCO* 0.74 (0.34–1.70) Max flow < 10 mL/s, % 21 Residual vol > 50 mL, % 12# Max capacity < 200 mL, % 6 † Median (range) * Obstruction coefficient # Chi-square, p=0.019 (RP cf LDRBT)	LDRBT / RP / p (chi-square) Emotional functioning 66±30 / 83±19 / 0.005 Global HRQoL 61±17 / 70±20 / 0.024 Values are mean ±SD
(Wyler et al 2009) Single centre, Switzerland Accrual: BT patients, March 2001 – December 2004 EBRT patients, January 2002 – December 2004	Prospective cohort Level III-2 interventional evidence Downs and Black quality score: **14/27** Overall quality assessment: **Poor**	**N: 212** consecutive patients with clinically localised prostate cancer LDRBT / RP N 70 / 142 Age, years 61 (49–75) / 64 (47–75) PSA, ng/mL 6.1 (1.1–12.8) / 11.3 (0.3–24) Gleason score 5.7 (4–7) / 6.3 (5–9)	**Global health and functional scales after RP and LDRBT** 5–12 months / 25–36 months / 37–53 months Global health: RP 71.7±27.4 / 80.6±11.4 / 77.8±9.6 LDRBT Cognitive functioning: RP 80±13.9 / 88.9±13.6* / 88.9±19.2 LDRBT 33.3±23.6 / 97.2±6.8* / 93.3±9.1 Emotional functioning:

Study	Study design and quality appraisal	Population	General health-related quality of life
		Clinical risk*, n Low 39 27 Intermediate 16 24 High 0 54 * Clinical risk was low (PSA < 10 ng/mL, stage T1c–T2a and GS < 7), intermediate (PSA 10–20 ng/mL or stage T2b or GS =7) or high (not defined). Only patients with prostate volume < 60 mL and urinary flow rate > 10 mL/s were selected. 79% of LDRBT patients and 74% of RP patients returned questionnaires.	RP 68.3±32.5 91.7±9.1 88.9±12.7 LDRBT 54.2±41.2 93.1±11.1 90±14.9 Physical functioning: RP 97.3±6 95.6±6.9 97.8±3.8 LDRBT 76.7±33 98.9±2.7 100±0 Role functioning: RP 80±27.4 97.2±6.8 100±0 LDRBT 66.7±47.1 100±0 100±0 Social functioning: RP 76.7±25.3 86.1±12.5 77.8±38.5 LDRBT 58.3±35.4 91.7±13.9 90±14.9 * significant difference between groups No changes in global health and function were observed within groups over time. *Comment:* *Data for 13–24 months follow-up were reported in the study but not included here. No significant differences in scores were observed between groups at 13–24 months follow-up.* **Symptom scales and single QoL items** 5–12 months 25–36 months p, within-group change‡ Appetite: RP 0 0 NS LDRBT 33.3±47.1 0 0.008 Dyspnoea: RP 6.7±14.9 5.6±13.6* NS LDRBT 33.3±47.1 0* NS Fatigue: RP 15.6±14.9 5.6±9.3 NS LDRBT 44.4±62.9 4.6±7.4 0.031 Nausea/vomiting : RP 0† 0 NS LDRBT 8.3±11.8† 2.8±6.8 0.037

Study	Study design and quality appraisal	Population	General health-related quality of life
			Pain: RP 16.7±23.6 0 NS LDRBT 33.3±47.1 8.3±13.9 NS Insomnia: RP 13.3±18.3 5.6±13.6 NS LDRBT 16.7±23.6 5.6±13.6 NS * Between-group comparison (Mann-Whitney U test), p=0.005 † Between-group comparison, p=0.037 ‡ Kruskal-Wallis test Data for 13–24 months and 37–53 months follow-up were reported in the study but not included here. No significant differences in scores seen between groups at 13–24 months or 37–53 months follow-up, or for change from the immediately preceding periods.

Table notes:
3D-CRT = three-dimensional conformal radiotherapy; ADT = androgen deprivation therapy; LDRBT = low-dose-rate brachytherapy; EBRT = external beam radiotherapy; EORTC QLQ – C30 = European Organisation for Research and Treatment of Cancer quality of life questionnaire; EPIC = Expanded Prostate cancer Index Composite; FACT-P = Functional Assessment of Cancer Therapy Prostate module; HRQoL = health-related quality of life; IMRT = intensity modulated radiotherapy; NS = not significant; NA = not assessed; RP = radical prostatectomy; SF-36 = Short Form–36 health survey; UCLA-PCI = University of California, Los Angeles – Prostate Cancer Index

Appendix H Data tables for primary and secondary effectiveness

Table 35 Studies comparing primary or secondary effectiveness outcomes for low-dose-rate brachytherapy, radical prostatectomy, external beam radiotherapy and active surveillance for the treatment of localised prostate cancer

Study	Study design and quality appraisal	Population	Effectiveness
(Giberti et al 2009) Single centre, Italy Accrual: May 1999 – October 2002	Randomised controlled trial Level II interventional evidence Downs and Black quality score: **19/27** Overall quality assessment: **Moderate**	**N: 100** RP patients and **100** LDRBT patients Questionnaires were completed for 89 RP patients and 85 LDRBT patients (ie 11 and 15 patients were lost to follow-up from the RP and LDRBT groups respectively). Exclusion criteria were in accordance with American Brachytherapy Society. RP: No. patients 100; Age, years 65.2 (57–74); Clinical stage: T1c (no. pts.) 64, T2a (no. pts) 36; Gleason score 5.9; PSA, ng/mL 7.8 (3.5–10) LDRBT: No. patients 100; Age, years 65.6 (56–74); Clinical stage: T1c (no. pts.) 59, T2a (no. pts) 41; Gleason score 5.7; PSA, ng/mL 7.5 (2.9–9.3) Values are mean (range) unless otherwise indicated	**Freedom from biochemical recurrence at 5 years** (n, %) RP: 81 (91) LDRBT: 78 (91.7) p-value: NR
(Zhou et al 2009) Multicentre, US Accrual: January 1999 – December 2001	Retrospective cohort Level III-2 interventional evidence Downs and Black quality score: **20/27** Overall quality assessment:	**N: 10,632** (more than 75% of these patients received combined therapy or 'no treatment', which was the reference) N: RP 936; LDRBT 644; EBRT 876	**Survival at 7 years*, percentage of patients** (Kaplan-Meier) Overall / Disease-specific RP: 89.0 / 97.9 LDRBT: 81.0 / 96.6 EBRT: 71.7 / 94.2

	Moderate	Age, years, n: 65–69 562 189 178 70–74 318 312 378 75+ 56 143 320 SEER stage, n (%) Local/regional 889 (95) 595 (92.4) 783 (89.4) Distant/ unknown 47 (5) 49 (7.6) 93 (10.6) Gleason score, n (%): < 7 714 (76.3) 531 (82.5) 674 (77) 7–10 177 (18.9) 53 (8.2) 135 (15.4) Unknown 45 (4.8) 60 (9.3) 67 (7.6)	**Survival at 7 years*** (Cox regression) Overall survival, hazard ratio† [95% CI] p-value Age (all categories) years 1.53 [1.45–1.61] <0.0001 Local stage Reference Regional stage 1.88 [1.58–2.24] <0.0001 Gleason score: 2–4 Reference NA 5–6 1.07 [0.90–1.27] 0.4434 7–10 1.48 [1.22–1.79] <0.0001 Unknown 1.35 [1.06–1.71] 0.0138 Treatment: None Reference NA RP 0.32 [0.25–0.41] <0.0001 LDRBT 0.40 [0.32–0.52] <0.0001 EBRT 0.63 [0.53–0.75] <0.0001 ADT 0.89 [0.80–0.98] 0.0243 Comorbidity: 0 Reference NA –1 0.64 [0.54–0.76] <0.0001 1 1.16 [0.97–1.38] 0.1101 2+ 1.83 [1.52–2.20] <0.0001 Disease-specific survival, hazard ratio† [95% CI] p-value Age (all categories) 1.49 [1.32–1.68] <0.0001 Local stage Reference NA Regional stage 4.06 [3.04–5.43] <0.0001 Gleason score: 2–4 Reference NA 5–6 1.53 [0.83–2.85] 0.1757 7–10 4.18 [2.23–7.81] <0.0001 Unknown 3.41 [1.69–6.88] 0.0006

			Treatment: None — Reference — NA RP — 0.25 [0.13–0.48] — <0.0001 LDRBT — 0.45 [0.23–0.87] — 0.0181 EBRT — 0.66 [0.41–1.04] — 0.0731 ADT — 1.32 [1.01–1.73] — 0.0445 Comorbidity: 0 — Reference — NA —1 — 0.82 [0.56–1.20] — 0.2976 1 — 0.68 [0.43–1.06] — 0.0895 2+ — 1.18 [0.73–1.89] — 0.4977 * Only patients with localised disease were considered. † Hazard ratio > 1 indicates a greater likelihood of dying, while a ratio of < 1 indicates increased likelihood of survival.
(Wong et al 2009) Single centre, US Accrual: May 1993 – July 2004	Retrospective cohort Level III-2 interventional evidence Downs and Black quality score: **19/27** Overall quality assessment: **Moderate**	**N:853** consecutive patients with localised prostate cancer* LDRBT n — 225 Clinical stage, n (%): T1 — 197 (88) T2 — 28 (12) PSA ≤ 10 ng/mL, n (%) — 193 (86) Gleason score ≤ 6, n (%) — 173 (77) Adjuvant hormone treatment, n (%) — 153 (68) Low risk , n (%) — 158 (70) 3D-EBRT — IMRT n — 270 — 314 Clinical stage, n (%): T1 — 120 (44) — 231 (74) T2 — 123 (46) — 69 (22) PSA ≤ ng/mL, n (%) — 92 (71) — 238 (76)	**Five-year biochemical-free recurrence among low-risk patients who did not have androgen deprivation therapy** Treatment — No. of patients — bNED (%) 3D-EBRT — 109 — 92 IMRT — 94 — 93 LDRBT — 116 — 97 p-value — 0.298

		Adjuvant hormone treatment, n (%) 47 (17) 114 (36) Low risk , n (%) 119 (44) 109 (35) Loss to follow-up: None evident. * See study profile for further details.	
(Beyer & Brachman 2000) Single centre, US Accrual: December 1988 – December 1995	Retrospective cohort Level III-2 interventional evidence Downs and Black quality score: **18/27** Overall quality assessment: **Moderate**	**N: 2,222** men with prostate cancer LDRBT EBRT n 695 1,527 Age, years* 74 74 PSA, ng/mL†: 0–4 128 (19) 132 (9) > 4–10 345 (50) 565 (37) > 10–20 144 (21) 481 (32) > 20 73 (10) 332 (22) Unknown 5 (< 1) 18 (1) Loss to follow-up: NA, results reported for all patients on database. * Median † Values are n (%) for each category shown	**Freedom from biochemical recurrence** (percentage of patients) LDRBT EBRT 5-year 7-year 5-year 7-year p-value* PSA, ng/mL 0–4 87 85 90 90 0.47 > 4–10 76 66 74 69 0.76 * p-value is for between-group comparison within each PSA stratum for both time points.
(Pickles et al 2010) Multicentre, Canada Accrual: July 1998 – January 2001.	Retrospective cohort Level III-2 interventional evidence Downs and Black quality score: **17/27** Overall quality assessment: **Moderate**	**N: 278** (139 LDRBT, 139 matched EBRT) LDRBT EBRT Age, years (range) 64 (48–79) 71 (54–84) PSA, ng/mL 5.6 6.4 Gleason score, %: ≤ 6 87.8 87.8 7 12.2 12.2 Risk group, %: Low 77.7 77.7 Intermediate 22.3 22.3 T-stage, % (2002):	**Freedom from biochemical recurrence at 5 years** (percentage of patients) LDRBT EBRT p (log rank) Risk group: Low risk 94 88 <0.001 Intermediate 100 78 ≤0.016 Overall 95.2 84.7 <0.001 **Other outcomes** LDRBT EBRT p-value Median PSA doubling time among patients with biochemical recurrence, months 6 24 0.01 Prostate cancer deaths, n 1 1 NR

		T1a–c 38.8 41.7 T2a 54 50.4 T2b 7.2 7.9 Percentage positive cores ≤ 50% † 87.8 87.8 ADT use, % 31.7 30.2 Mean duration, months 6 5.8 No PSA data during follow-up 10 8 Radiation dose, Gy 144 68 Values are median unless otherwise specified. † Data available for 33% of patients EBRT dosimetry, Gy: < 66 5% 66 23% 68 46% > 68 25%	Non-prostate cancer deaths†, % 4 18 0.001 † 8-year projection
(Vicini et al 2002) Multicentre, US and Germany Accrual: 1989–1998	Comparison of two matched single arms Level III-3 interventional evidence Downs and Black quality score: **12/27** Overall quality assessment: **Poor**	**N: 6,877** men with prostate cancer of whom 5,179 are not considered for this analysis, leaving data for 1,698 patients treated with LDRBT (537), 3D-EBRT (670) and RP (491)—see study profile for further details Age (range), years 61–73 Median follow-up, months 38 PSA, ng/mL ≤ 6 Gleason score (range) 5–6	**Effectiveness** Five-year outcomes (percentage of patients): bNED / Overall survival LDRBT Centre 1: 82 / 83 LDRBT Centre 2: 89 / NR 3D-EBRT: 85 / NR EBRT: 71 / 85 RP: 97 / 97

Table notes:
LDRBT = low-dose-rate brachytherapy; EBRT = external beam radiotherapy; RP = radical prostatectomy; IMRT = intensity modulated radiotherapy; PSA = prostate specific antigen; NA = not applicable; bNED = biochemical freedom from recurrence; NR = not reported

Appendix I Data tables for economic considerations

Table 36 Economic considerations of low-dose-rate brachytherapy compared with radical prostatectomy, external beam radiotherapy and active surveillance for the treatment of localised prostate cancer

Study	Study design and quality appraisal	Population	Cost
(Buron et al 2007) Multicentre study, France Accrual: March 2001 – June 2002	Prospective cohort Level III-2 interventional evidence Downs and Black quality score: **17/27** Overall quality assessment: **Moderate**	**N: 435** men with low-risk prostate cancer from 11 French hospitals treated with LDRBT (308) or RP (127) RP / LDRBT Age, years: 62.7±6 / 65.2±6.3 Neoadjuvant hormones, %: 6.3 / 43.5 IPSS: 7.8 / 5.9 Values are mean±standard deviation. Loss to follow-up after 24 months was between 35% and 59% (N data not provided) depending on treatment arm—see study profile for further details. Values are mean±standard deviation, unless otherwise specified	**Mean hospital costs** (2001 euros) RP / LDRBT / Mean difference Initial treatment costs: Consumables: 410 [288,533] / 5,192 [5025,5360] / 4,782* [4510,5054] Operating theatre: 1,674 [1602,1745] / 752 [642,863] / –922* [–1099,–744] Hospitalisations: 4,387 [4150,4625] / 1,060 [1011,1110] / –3,327* [–3497,–3157] Post-operative CT: † / 155 / † Total: 6,472 [6206,6737] / 7,159 [6939,7380] / 687* [305,1071] Hospital follow-up costs: 2 months: 387 [76,699] / 47 [0,93] / –340* [–552,–129] 6 months: 610 [247,972] / 64 [14,114] / –546* [–790,–302] 12 months: 775 [386,1164] / 88 [32,145] / –687* [–950,–424] 18 months: 874 [477,1271] / 246 [73,421] / –628* [–998,–258] 24 months: 992 [565,1418] / 268 [93,443] / –724* [–1108,–340] Hospital costs: 2 months: 6,859 [6403,7315] / 7,206 [6973,7438] / 347 [117,811]

Study	Study design and quality appraisal	Population	Cost			
			6 months	7,081 [6577,7586]	7,223 [6990,7457]	142 [–343,627]
			12 months	7,247 [6717,7777]	7,248 [7014,7481]	1 [–495,497]
			18 months	7,346 [6818,7873]	7,406 [7123,7688]	60 [–493,613]
			24 months	7,463 [6916,8010]	7,427 [7144,7710]	–36 [–597,525]
			Mean outpatient costs (2001 euros)			
				RP	LDRBT	Mean difference
			2 months	118 [93,144]	243 [219,267]	125* [83,167]
			6 months	224 [178,269]	290 [264,316]	66* [15,118]
			12 months	289 [233,346]	346 [315,377]	57 [5,118]
			18 months	356 [289,423]	420 [378,461]	64 [–15,144]
			24 months	419 [343,494]	482 [435,528]	63 [–29,152]
			Mean costs due to loss of productivity in working patients (2001 euros)			
				RP	LDRBT	Mean difference
			2 months	2,012 [1368,2656]	487 [105,869]	–1,525* [–2213,–837]
			6 months	2,667 [1710,3625]	568 [112,1023]	–2,099* [–3024,–1175]
			12 months	3,514 [1810,5217]	588 [123,1053]	–2,926* [–4319,–1532]
			18 months‡	3,514 [1810,5217]	588 [123,1053]	–2,926* [–4319,–1532]

Study	Study design and quality appraisal	Population	Cost
			24 months 3,678 [1774,5581] 620 [153,1086] –3,058 [–4586,–1530] **Mean societal costs** (2001 euros) RP / LDRBT / Mean difference 2 months 7,465 [6966,7964] / 7,525 [7264,7785] / 60 [–455,575] 6 months 7,930 [7304,8555] / 7,616 [7349,7882] / –314 [–888,261] 12 months 8,353 [7612,9093] / 7,702 [7432,7971] / –651 [–1282,20] 18 months 8,506 [7771,9242] / 7,929 [7616,8243] / –577 [–1253,99] 24 months 8,715 [7933,9496] / 8,019 [7704,8334] / –696 [–1394,2] * Statistically significant difference † Reason for missing data unclear. ‡ Not clear why these results are identical to 12-month results— possibility of error in reporting.
(Ciezki et al 2000) Single centre, US Accrual: January 1997 – October 1998	Prospective cohort Level III-2 interventional evidence Downs and Black quality score: **17/27** Overall quality assessment: **Moderate**	**N: 583** consecutive men with clinically localised prostate cancer underwent retropubic RP (404) or LDRBT (179) Tumour grade, clinical stage, preoperative PSA, age and comorbidity were evenly distributed between the groups. Majority of patients had PSA < 10 ng/mL, Gleason score ≤ 6 and stage T1 or T2a disease.	**Categorical technical costs for RP vs LDRBT** (relative cost ratios) RP / LDRBT (pre-plan) / LDRBT (real-time) Category: Anaesthesiology 1.0 / 0.44 / 0.56 Laboratory medicine 1.0 / 0.01 / 0.01 Pharmacy 1.0 / 0.11 / 0.13 Operating room nursing 1.0 / 0.49 / 0.67 Floor nursing 1.0 / 0.07 / 0.13 Radiology 1.0 / 17.1 / 13.8

Study	Study design and quality appraisal	Population	Cost
			Total costs for RP vs LDRBT (relative cost ratios) RP: 1.0 / LDRBT (pre-plan): 0.36 / LDRBT (real-time): 0.42 Category: Technical cost Excluding seeds: 1.0 / 0.36 / 0.42 Including seeds: 1.0 / 2.16 / 2.58 Professional cost: 1.0 / 0.97 / 1.02 Total cost: 1.0 / 1.85 / 2.05
(Kohan et al 2000) Single centre, US Accrual: June 1995 – September 1996	Prospective cohort Level III-2 interventional evidence Downs and Black quality score: **15/27** Overall quality assessment: **Poor**	**N: 60** consecutive men with clinically localised prostate cancer (T1–T2, N0, M0) underwent RP (38) and LDRBT with ^{125}I (13) or ^{103}Pd (9) RP / LDRBT Age, years (range): 61.2 (43–71) / 71.1 (60–86) PSA, ng/mL: 8.4 (2.2–34) (2.2–34) / 12 (2.3–37.7) Gleason score: 6 (4–8) / 6 (4–8)	**Charge comparison for RP and LDRBT** (US$) RP / LDRBT Pre-operative charges: 1,526.20 / 1,801.20 Operative charges: 11,352.59 / 9,818.17* Post-operative charges: 1,007.20 / 2,285.20* Total charges: 13,904.60 / 13,886 * p<0.05 **Charge comparison for LDRBT** (US$) ^{125}I / ^{103}Pd Pre-operative charges: 1,154.65 / 2,735.18† Post-operative charges: 2,548.50 / 1,904.79 † p<0.01 Data were stratified by radioactive source; however, no statistical analysis was performed comparing cost of ^{125}I LDRBT with RP and therefore conclusions regarding the cost-efficacy of ^{125}I LDRBT compared to RP are

Study	Study design and quality appraisal	Population	Cost
			difficult. Conclusions are further inhibited due to the bias inherent in charge variation between institutions and the age of the data collected during 1995–96.
(Ollendorf et al 2009a) Health technology assessment, US Patient accrual is varied (HTA is based on three separate systematic reviews). Included studies were published between January 1996 – May 2009 for RP and AS; 1995 – August 2008 for IMRT; and 1995 – August 2008 for LDRBT (the LDRBT systematic review also updated the IMRT review).	Health technology assessment (HTA) Level of evidence for this HTA cannot be assessed. The systematic reviews on which the HTA is based rely primarily on non-comparative evidence (level IV). Quality: good (Drummond & Jefferson 1996)	**Adverse event rates** The HTA used adverse event rates from systematic reviews, which required included studies to contain 'a preponderance' of patients of clinical stage T1–T2a, Gleason score ≤ 6 and PSA < 10 ng/mL. However, studies including intermediate-risk patients were not excluded. Baseline adverse event rates were taken from Bacon et al (2003) and Andersson et al (2004). **Patient utilities** Dale et al (2008); Stewart et al (2005); Sullivan & Ghushchyan (2006) **Transition probabilities** Alibhai et al (2003); D'Amico et al (1999); Horwitz et al (2005) **Costs** US Medicare and other sources	**Cost–utility analysis** Comparison of LDRBT, IMRT, AS and RP Base case presented in the text—see Table 13.

Table notes:
AS = active surveillance; LDRBT = low-dose-rate brachytherapy; EBRT = external beam radiotherapy; HTA = health technology assessment; IMRT = intensity modulated radiotherapy; PSA = prostate specific antigen; QALY = quality adjusted life year; RP = radical prostatectomy

Appendix J Studies included in the review

Profiles of included studies on safety and effectiveness

Author & year, location and accrual period	Level of evidence and quality assessment	Study design	Study population (inclusion/exclusion criteria)	Intervention	Outcomes assessed (relevant to this review)	Duration of follow-up
(Giberti et al 2009) Single centre, Italy Accrual: May 1999 – October 2002	Level II interventional evidence Downs and Black quality score: **19/27** Overall quality assessment: **Moderate**	Randomised controlled trial	**N: 100** RP patients and **100** LDRBT patients Questionnaires were completed for 89 RP patients and 85 LDRBT patients (ie 11 and 15 patients were lost to follow-up from the RP and LDRBT groups respectively). Exclusion criteria were in accordance with American Brachytherapy Society. RP / LDRBT No. patients: 100 / 100 Age, years (range): 65.2 (57–74) / 65.6 (56–74) Clinical stage: T1c (no. pts): 64 / 59 T2a (no. pts): 36 / 41 Gleason score: 5.9 / 5.7 PSA, ng/mL: 7.8 (3.5–10) / 7.5 (2.9–9.3) Values are mean (range) unless otherwise indicated.	**Intervention**: LDRBT with D90 > 140 Gy considered the cut-off to predict good-quality implant **Comparato**r: RP with bilateral nerve sparing performed for all patients	**Safety** Urinary, bowel and sexual function Urinary and erectile function were assessed using IPSS and IIEF-5 questionnaires. Urinary and bowel symptoms, sexual function and activity were measured using relevant domains of EORTC-QLQ and PR25. General HRQoL General QoL was assessed using EORTC-QLQ.	5 years
(Lee et al 2001) Single institution, US. Accrual: May 1998 – June 1999	Level III-2 interventional evidence Downs and Black quality score: **22/27** Overall quality assessment:	Prospective cohort	**N: 90** All patients treated between May 1998 and June 1999 (n=98) were offered enrolment. 90 patients (91%) agreed to complete the FACT-P and IPSS questionnaires. LDRBT	**Intervention:** 2-stage (pre-operative planning) ^{125}I LDRBT, prescribed to 144 Gy (TG43) **Comparators:** 10 MV photon 3D-CRT	**Safety** General HRQoL FACT-P was collected and compared between treatment groups at baseline, 1 month, 3 months and 12 months.	1 year

Author & year, location and accrual period	Level of evidence and quality assessment	Study design	Study population (inclusion/exclusion criteria)		Intervention	Outcomes assessed (relevant to this review)	Duration of follow-up
	Moderate		N	44	prescribed to 70.2 – 72 Gy to 95% of the volume in 1.8 Gy fractions using a four-field technique. Retropubic prostatectomy with nerve sparing performed at the discretion of the operating surgeon. Pelvic lymph dissection was routinely performed.		
			Age, years	67.1 (49–79)			
			Stage, n (%)				
			T1 T2	26 (59) 18 (41)			
			PSA, ng/mL	6.5 (1.3–13.5)			
			Gleason score n (%)				
			≤ 6 7 > 7	38 (86)† 6 (14) 0 (0)			
				EBRT			
			N	23			
			Age, years	68.8 (51–79)			
			Stage, n (%):				
			T1 T2	12 (52) 11 (48)			
			PSA, ng/mL	8.1 (2.9–19.6)			
			Gleason score n (%)				
			≤ 6 7 > 7	11 (48) 10 (43) 2 (9)			
				RP			
			N	23			
			Age, years	61.0 (42–68)*			
			Stage, n (%)				
			T1 T2	19 (83) 4 (17)			
			PSA, ng/mL	6.2 (1.3–12.0)			

Author & year, location and accrual period	Level of evidence and quality assessment	Study design	Study population (inclusion/exclusion criteria)	Intervention	Outcomes assessed (relevant to this review)	Duration of follow-up
			Gleason score n (%) ≤ 6 16 (70) 7 5 (22) > 7 2 (9) Values are median (range) or n (%) † significantly more Gleason ≤ 6 than RP or EBRT (p=0.015); * significantly younger than LDRBT or EBRT (p=0.0006).			
(Zhou et al 2009) Multicentre, US Accrual: January 1999 – December 2001	Level III-2 interventional evidence Downs and Black quality score: **20/27** Overall quality assessment: **Moderate**	Retrospective cohort	**N: 10,632** (more than 75% of these patients received combined therapy or 'no treatment', which was the reference) RP / LDRBT / EBRT N 936 / 644 / 876 Age, n, years: 65–69 562 / 189 / 178 70–74 318 / 312 / 378 75+ 56 / 143 / 320 SEER stage, n (%): Local/regional 889 (95) / 595 (92.4) / 783 (89.4) Distant/ unknown 47 (5) / 49 (7.6) / 93 (10.6) Gleason score, n (%): < 7 714 (76.3) / 531 (82.5) / 674 (77) 7–10 177 (18.9) / 53 (8.2) / 135 (15.4) Unknown 45 (4.8) / 60 (9.3) / 67 (7.6) All categories vary significantly with treatment (chi-square p<0.001)	**Intervention:** LDRBT **Comparators:** RP and EBRT Treatment details are not provided and are likely to vary between centres.	**Effectiveness** Kaplan-Meier overall and disease-specific survival at 7 years post treatment Cox regression analyses of overall and disease specific survival controlling for age, race, tumour stage, Gleason score, pre-treatment comorbidity and treatment	7 years

Author & year, location and accrual period	Level of evidence and quality assessment	Study design	Study population (inclusion/exclusion criteria)	Intervention	Outcomes assessed (relevant to this review)	Duration of follow-up
			453 patients excluded because they were diagnosed with prostate cancer on or after their date of death, leaving 10,179 patients. Only 2,456 patients were treated with RP, LDRBT or EBRT monotherapy. Eligibility of other patient groups for this analysis is uncertain. Population defined as all men aged 65 years or older residing in Ohio, diagnosed with incident prostate cancer during 1999–2001.			
(Eade et al 2008) Single centre, US Accrual: LDRBT patients, May 1998 – August 2004 EBRT patients, August 2001 – June 2004	Level III-2 interventional evidence Downs and Black quality score: **19/27** Overall quality assessment**: Moderate**	Prospective cohort	**N: 374** low-risk prostate cancer patients (as defined by American Joint Committee on Cancer) with Gleason score < 7 EBRT / LDRBT N: 216 / 158 Age, years: 67.6 (27–81)* / 64.7 (42–78) PSA, ng/mL: 5.2 (0.4–9.6) / 5.2 (0.5–9.8) * Values are median (range) Clinical stage, n (%): T1c: 169 (78.2) / 134 (83.5) T2a: 33 (15.3) / 26 (16.5) T2b: 14 (6.5) / 0 No patients were lost to follow-up.	**Intervention**: LDRBT with prescription dose of 145 Gy using real-time planning **Comparator**: EBRT with prescription dose of 74–78 Gy delivered in daily fractions of 2.0 Gy; rectal volume receiving > 65 Gy and > 40 Gy limited to < 7% and < 35% respectively; bladder volume receiving > 65 Gy and > 40 Gy limited to < 25% and < 50% respectively	**Safety** Acute and late gastrointestinal and genitourinary side effects were recorded using modified Radiation Therapy Oncology Group RTOG scale. Number of urethral strictures were also recorded.	Mean, months LDRBT: 48 EBRT: 43
(Wong et al 2009) Single centre, US Accrual: May 1993 – July 2004	Level III-2 interventional evidence Downs and Black quality score: **19/27** Overall quality assessment:	Retrospective cohort	**N:853** consecutive patients with localised prostate cancer* LDRBT n: 225 Clinical stage, n(%): T1: 197 (88)	**Intervention:** Pre-planned LDRBT using either iodine (peripheral dosage of 144 Gy) or palladium (120 Gy) 106 patients in total received monotherapy	**Safety** Acute and Late RTOG gastrointestinal and genitourinary side effects (maximum score at any time following treatment) **Effectiveness** Five-year disease-free recurrence was calculated using the Kaplan-Meier product limit method.	Median, months LDRBT, 58 3D-EBRT, 62 IMRT, 56

Author & year, location and accrual period	Level of evidence and quality assessment	Study design	Study population (inclusion/exclusion criteria)	Intervention	Outcomes assessed (relevant to this review)	Duration of follow-up
	Moderate		T2 28 (12) T3 0 PSA, ng/mL, n (%): ≤ 10 193 (86) 10.1–20 28 (12) > 20 4 (2) Gleason score, n (%): ≤ 6 173 (77) ≥ 7 52 (23) Adjuvant hormone treatment, n (%): No 153 (68) Yes 72 (32) Risk group, n (%): Low 158 (70) Intermediate 58 (26) High 9 (4) 3D-EBRT / IMRT n 270 / 314 Clinical stage, n (%): T1 120 (44) / 231 (74) T2 123 (46) / 69 (22) T3 27 (10) / 14 (4) PSA, ng/mL, n (%): ≤ 10 192 (71) / 238 (76) 10.1–20 52 (19) / 54 (17) ≥ 20 26 (10) / 22 (7) Adjuvant hormone treatment, n (%): No 223 (83) / 200 (64) Yes 47 (17) / 114 (36)	with iodine and their unknown distribution among the risk groups makes it uncertain (however probable) if the majority of low-risk patients received iodine implants. **Comparators:** 3D conformal EBRT at a median prostate dosage of 68.4 Gy delivered daily fractions of 1.8–2.0. Intensity modulated EBRT at a median prostate dosage of 75.6 Gy		IDRBT, 49

Author & year, location and accrual period	Level of evidence and quality assessment	Study design	Study population (inclusion/exclusion criteria)	Intervention	Outcomes assessed (relevant to this review)	Duration of follow-up
			Risk group, n (%): Low 119 (44) 109 (35) Intermediate 111 (41) 151 (48) High 40 (15) 54 (17) Loss to follow-up: None evident. * Only patients with low-risk disease (stage T1–T2, PSA ≤ 10 ng/mL, Gleason score ≤ 6) were considered eligible and, of these, only those who *did not* receive androgen deprivation therapy had results for which relevant data could be extracted. Results for patients who received combination EBRT and LDRBT (n=44) were not considered.			
(Beyer & Brachman 2000) Single centre, US Accrual: December 1988 – December 1995	Level III-2 interventional evidence Downs and Black quality score: **18/27** Overall quality assessment: **Moderate**	Retrospective cohort	**N: 2,222** men with prostate cancer LDRBT EBRT n 695 1527 Age, years* 74 74 PSA, ng/mL†: 0–4 128 (19) 132 (9) > 4–10 345 (50) 565 (37) > 10–20 144 (21) 481 (32) > 20 73 (10) 332 (22) Unknown 5 (< 1) 18 (1) Gleason score†: 2–4 145 (21) 434 (28) 5–6 433 (63) 705 (46) 7 85 (13) 268 (18) 8–10 20 (3) 116 (8) Unknown 12 (2) 5 (< 1) Clinical stage†: T1 117 (17) 290 (19)	**Intervention**: LDRBT with a prescribed dose of either 160 Gy or 120 Gy, depending on whether iodine or palladium seeds were used—663 (95%) and 32 (5%) patients respectively All cases were undertaken prior to TG43 guidelines. **Comparator**: EBRT at median dose of 66.6 (range 14.4–72.0) Gy	**Effectiveness** 5- and 7-year biochemical free recurrence was reported according to PSA category, as indicated in the 'Study population' column. Only outcomes for patients with PSA ≤ 10 ng/mL are considered.	Median, months LDRBT: 41.3 EBRT: 51.3

Author & year, location and accrual period	Level of evidence and quality assessment	Study design	Study population (inclusion/exclusion criteria)	Intervention	Outcomes assessed (relevant to this review)	Duration of follow-up
			T2 578 (83) 1238 (81) Loss to follow-up: NA, results reported for all patients on database. * Median † Values are n (%) for each category shown.			
(Litwin et al 2004) Multicentre, US Accrual period is not reported.	Level III-2 interventional evidence Downs and Black quality score: **18/27** Overall quality assessment: **Moderate**	Prospective cohort study	**N: 1,584** consecutively recruited patients from 31 community- and academic-based urology practices All patients must have consented, and have been treated with RP, EBRT or LDRBT within the first 6 months of diagnosis. RP (n=1,276) Age, years 61.2±6.8 Follow-up, months 14.3±8.2 Time to 1st assessment months 3.5±2.8 Gleason score, %: 2–6 78 7 19 8–10 4 Clinical stage, %: cT1 42 cT2 55 cT3 2 EBRT (n=99) Age, years 70.9±6.1 Follow-up, months 16.1±8.4 Time to 1st assessment, months 2.8±2.2 Gleason score, %:	**Intervention:** LDRBT monotherapy **Comparators:** RP and EBRT	**Safety** Bowel function and bowel bother following treatment (every 3–6 months) measured by the University of California and Los Angeles (UCLA) Prostate Cancer Index (PCI)	Mean, months RP: 14.3±8.2 EBRT: 16.1±8.4 LDRBT: 13.4±7.7

Author & year, location and accrual period	Level of evidence and quality assessment	Study design	Study population (inclusion/exclusion criteria)	Intervention	Outcomes assessed (relevant to this review)	Duration of follow-up
			2–6 67 7 25 8–10 8 Clinical stage, %: cT1 (%) 44 cT2 (%) 52 cT3 (%) 3 LDRBT (n=209) Age, years 68.6±7.4 Follow-up, months 13.4±7.7 Time to 1st assessment months 4.2±3.1 Gleason score, %: 2–6 89 7 9 8–10 1 Clinical stage, %: cT1 (%) 43 cT2 (%) 57 cT3 (%) 0 Values are mean±SD unless otherwise specified.			
(Buron, Le Vu et al. 2007) Multicentre, France Accrual: March 2001 – June 2002	Level III-2 Quality: Reporting 8/11 Ex Valid 1/3 Bias 4/7 Confounding 3/6 **Total 16/27**	Prospective cohort	**N: 435** men with low-risk prostate cancer from 11 French hospitals treated with LDRBT (308) or RP (127) RP LDRBT Age, years 62.7±6 65.2±6.3 Neoadjuvant hormones, % 6.3 43.5 Clinical stage, %:	**Intervention**: LDRBT with prescribed dose of 145 Gy and mean rectal volume of 1.4 cc receiving 145 Gy; 243 patients treated using real-time planning while the remaining 65 underwent pre-planning	**Safety** <u>Urinary, bowel and sexual function</u> Outcomes were assessed using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) prostate cancer specific (PR-25) module. Outcomes were obtained at seven time points during follow-up: pre-treatment, immediate post-treatment, and 2, 6, 12, 18 and 24 months following	Mean, months LDRBT: 25.8 RP: 25

Author & year, location and accrual period	Level of evidence and quality assessment	Study design	Study population (inclusion/exclusion criteria)	Intervention	Outcomes assessed (relevant to this review)	Duration of follow-up
			T1 52.8 64.8 T2 47.2 35.2 PSA, ng/mL 8.9±4 7.5±2.7 Gleason score 5.9±1.1 5.5±1.1 IPSS 7.8 5.9 Response rate, %: Before treatment 89 94 Immediately after treatment 70 85 2 months 72 85 6 months 57 78 12 months 47 63 18 months 39 60 24 months 41 65 Values are mean±standard deviation, unless otherwise specified.	**Comparator**: RP (retropubic)	treatment. General HRQoL EORTC-QLQ was used to assess general QoL outcomes before and after treatment at each of the study follow-up points. Cost Initial treatment, hospital follow-up, outpatient and production loss costs were prospectively collected and analysed.	
(Ciezki et al 2000) Single centre, US Accrual: January 1997 – October 1998	Level III-2 interventional evidence Downs and Black quality score: **17/27** Overall quality assessment: **Moderate**	Prospective cohort	**N: 583** consecutive men with clinically localised prostate cancer underwent retropubic RP (404) or LDRBT (179). Tumour grade, clinical stage, preoperative PSA, age and comorbidity were evenly distributed between the groups. Majority of patients had PSA < 10 ng/mL, Gleason score ≤ 6 and stage T1 or T2a disease.	**Intervention:** LDRBT with either real-time or pre-planning techniques **Comparator:** RP (retropubic)	**Cost** Technical and professional (perioperative) costs from a hospital-wide accounting system were used to generate cost ratios for a comparison of LDRBT (real-time and pre-planning procedures) and RP.	NA
(Ferrer et al 2008) Multicentre, Spain Accrual: April 2003 – March 2005	Level III-2 interventional evidence Downs and Black quality score: **17/27**	Prospective cohort	**N: 841** organ-confined prostate cancer patients RP EBRT LDRBT Age, years 64±5.5 69.2±5.5 66.9±6.5	**Intervention**: LDRBT with prescription dose of 144 Gy according to TG43	**Safety** Urinary, bowel and sexual function HRQoL questionnaires* were administered before and after (1,3, 6, 12 and 24 months) treatment * Expanded Prostate Cancer Index Composite	2 years

Author & year, location and accrual period	Level of evidence and quality assessment	Study design	Study population (inclusion/exclusion criteria)	Intervention	Outcomes assessed (relevant to this review)	Duration of follow-up
	Overall quality assessment: **Moderate**		PSA, ng/mL 7.9±3.3 10.1±7.9 6.9±2.3 Gleason score 6.8±6.2 6±1.1 5.7±4.4 Values are mean±standard deviation. Clinical stage, n (%): T1 88 (65.7) 106 (51.7) 224 (81.5) T2 46 (34.3) 95 (46.3) 51 (18.5) Tx 0 4 (2) 0 Risk group*, n (%): Low 58 (43.3) 98 (47.8) 241 (87.6) Intermed. 71 (53) 70 (34.1) 32 (11.6) High 5 (3.7) 37 (18) 2 (0.7) Loss to follow-up: 614 patients treated with LDRBT (275), RP (134) and EBRT (205) were included in HRQoL analysis. * Risk groups: Low (T1c or T2a, PSA < 10 ng/mL and Gleason score < 6), intermediate (Intermediate; T2b, PSA 11–20 ng/mL, or Gleason score = 7) and high (T2c, PSA > 20 ng/mL or Gleason score > 7) Only outcomes for low-risk patients were considered for the purposes of this assessment.	**Comparators**: EBRT using 3D conformal technique with mean dose of 74 Gy in 1.8–2.0 Gy daily fractions RP with some cases of nerve sparing at the discretion of the operating surgeon	(EPIC) and the American Urological Association Symptom Index (AUA) <u>General HRQoL</u> General QoL and non-prostate (general) cancer specific outcomes were obtained using Functional Assessment of Cancer Therapy (FACT-G) and the Medical Outcomes Study 36-Item Short Form (SF-36). FACT-P (prostate-specific items) data were collected and are included under general QoL for this assessment since scores could not be split into urinary, bowel, and sexual components.	
(Hashine et al 2008) Single centre, Japan	Level III-2 interventional evidence Downs and Black quality score: **17/27**	Prospective cohort	**N: 213** (131 RP and 82 LDRBT patients) 122 respondents in RP arm, patient characteristics only provided for responders	**Intervention:** Two-stage (pre-operative planning) ^{125}I LDRBT, prescribed to 145 Gy	**Safety** <u>Urinary function</u> Functional outcomes as measured using the University of California and Los Angeles (UCLA)	1 year

Author & year, location and accrual period	Level of evidence and quality assessment	Study design	Study population (inclusion/exclusion criteria)	Intervention	Outcomes assessed (relevant to this review)	Duration of follow-up
Accrual: January 2003 – July 2005	Overall quality assessment: **Moderate**		RP / LDRBT / p-value Age, years* (range): 68.0 (42–78) / 70.5 (50–85) / 0.016 Clinical stage, n: / / 0.008 T1: 79 / 66 T2: 33 / 16 T3: 10 / 0 PSA, ng/mL*: 9.6 / 6.7 / <0.001 Gleason score, n: / / <0.001 5–6: 44 / 51 7: 42 / 27 8–10: 36 / 4 Neoadjuvant hormones: 8 / 18 / 0.002 Nerve sparing: 22 / - EBRT: - / 1 *Median	**Comparator:** Retropubic RP as described by Walsh performed by two urologists	Prostate Cancer Index (PCI) at baseline and 1, 3, 6 and 12 months following treatment. UCLA-PCI measures urological, bowel and sexual function outcomes, and the bother associated with each outcome. General HRQoL Quality of life outcomes as measured by the medical outcomes study Short Form (SF-36). SF-36 measures HRQoL in eight domains: physical functioning, role physical, body pain, general health, vitality, social functioning, role emotional and mental health. Outcomes were measured at baseline, 1, 3, 6 and 12 months.	
(Pickles et al 2010) Multicentre, Canada Accrual: July 1998 – January 2001.	Level III-2 interventional evidence Downs and Black quality score: **17/27** Overall quality assessment: **Moderate**	Retrospective cohort	**N: 278** (139 LDRBT, 139 matched EBRT) LDRBT / EBRT Age, years (range): 64 (48–79) / 71 (54–84) PSA, ng/mL: 5.6 / 6.4 Gleason score, %: ≤ 6: 87.8 / 87.8 7: 12.2 / 12.2 Risk group, %: Low: 77.7 / 77.7 Intermediate: 22.3 / 22.3	**Intervention:** One-stage (intra-operative planning) ^{125}I LDRBT planned to a minimum peripheral dose of 144 Gy with post-implant dosimetry at day 30. Patients with Gleason 7 or Gleason 6 and PSA > 10 and ≤ 15 were given ADT 3 months before implant continuing for 3 months following	**Effectiveness** Freedom from biochemical recurrence (defined by the Phoenix definition) Quality assurance was used to ensure a true recurrence rather than a PSA 'bounce'. Overall survival and prostate cancer specific survival were assessed. The use of ADT following treatment (not continuing adjuvant therapy) was also measured as a surrogate for progressing disease. **Safety** Late treatment side effects (urinary and bowel side effects) were measured using the Radiation	Median, months LDRBT: 68 EBRT: 67

Author & year, location and accrual period	Level of evidence and quality assessment	Study design	Study population (inclusion/exclusion criteria)	Intervention	Outcomes assessed (relevant to this review)	Duration of follow-up
			Clinical stage, % (2002): T1a–c 38.8 41.7 T2a 54 50.4 T2b 7.2 7.9 Per cent positive cores ≤ 50% † 87.8 87.8 ADT use, % 31.7 30.2 Mean duration (months) 6 5.8 No PSA data during follow-up 10 8 Radiation dose, Gy 144 68 Values are median unless otherwise specified. † Data available for 33% of patients EBRT dosimetry: < 66 Gy 5% 66 Gy 23% 68 Gy 46% > 68 Gy 25% All patients were treated between 1998 and 2001, and were matched on PSA level (within 1 ng/mL), same Gleason category (≤ 6 or 7), clinical stage (T1 or T2), same percentage positive biopsy cores (when available, > or ≤ 50%), and the same use and duration of ADT (No or Yes, duration within 3 months). When matches could not be obtained, patients were discarded from the analysis. Matching occurred without knowledge of	implant. Patients with large prostate glands (> 40 cc in the first year of the study and > 50 cc thereafter) were also given 6 months of ADT as above. **Comparator:** 3D-Conformal radiotherapy treated to doses in the range 52.5–72.0 Gy (five patients received 52.5 Gy in 20 fractions).	Therapy Oncology Group (RTOG) toxicity scale. Late side effects are defined as those occurring at least 1 year from LDRBT implant or at least 6 months following the end of EBRT treatment.	

Author & year, location and accrual period	Level of evidence and quality assessment	Study design	Study population (inclusion/exclusion criteria)	Intervention	Outcomes assessed (relevant to this review)	Duration of follow-up
			patient outcome (and was facilitated by database software). Eligibility for LDRBT was more stringent and therefore LDRBT criteria were applied to EBRT patients. 394 treated with LDRBT. 1,369 treated with EBRT, 667 entered onto the EBRT database, 207 met the eligibility criteria. 139 LDRBT patients successfully matched 1:1 with EBRT patients.			
(Smith et al 2010) Population-based, NSW, Australia Accrual: October 2000 – May 2003	Level III-2 interventional evidence Downs and Black quality score: **17/27** Overall quality assessment: **Moderate**	Prospective cohort	**N: 4,542** men (3,195 with histologically confirmed T1a–2c prostate cancer plus 1,347 controls with no diagnosis of prostate cancer, as indicated and cross-checked by registry data) All potential participants had to be physically and mentally capable of a 30-minute telephone interview in English. Potentially eligible: Cases 3,195; Controls 1,347 Final analysis: Cases 1,636; Controls 495 AS: Cases 200; Controls NA RP: Cases 981; Controls NA EBRT: Cases 123; Controls NA Combined EBRT/ADT: Cases 166; Controls NA LDRBT: Cases 58; Controls NA Mean age, years: Cases 61.2; Controls 61.2	**Intervention**: AS, RP, EBRT, LDRBT, ADT, combined EBRT/ADT **Comparator**: Follow-up of healthy controls, matched by age and residence from the NSW electoral role	**Safety** Telephone interview conducted to assess: <u>Urinary, bowel and sexual function</u> HRQoL measured using domain-specific items for urinary, bowel and sexual function according to the long form University of California, Los Angeles (UCLA) prostate cancer index (adapted). <u>General HRQoL</u> Physical and mental component scores were also collected using the UCLA prostate cancer index (adapted).	3 years

Author & year, location and accrual period	Level of evidence and quality assessment	Study design	Study population (inclusion/exclusion criteria)	Intervention	Outcomes assessed (relevant to this review)	Duration of follow-up
			[95% CI] [60.7, 61.7] [61, 61.5]			
(Frank et al 2007) Single centre, US Accrual: 1998 – 2000	Level III-2 interventional evidence Downs and Black quality score: **16/27** Overall quality assessment: **Moderate**	Retrospective cohort	**N: 960** men treated with LDRBT (160), RP (400) and HDR EBRT (400) LDRBT RP EBRT Age, years* 64 61 68 Loss to follow-up, n (%) 86 (54) 166 (41) 265 (66) * Values are median Only patients treated with monotherapy were eligible for inclusion 97% of patients had T1–2 disease and Gleason score < 7	**Intervention**: LDRBT with prescribed dose of 145 Gy **Comparators**: EBRT with prescribed dose of 78 Gy RP with some cases of nerve sparing at surgeon discretion	**Safety** Urinary, bowel and sexual function HRQoL measured using mailed Extended Prostate Index Composite (EPIC) surveys Retrospective analysis meant that no baseline HRQoL data were available for comparison with post-treatment data, and only a one-point-in-time between-group comparison was made.	Median, years LDRBT: 3.5 RP: 4 EBRT: 4.7
(Guedea et al 2009) Single centre, Spain April 2003 – March 2005	Level III-2 interventional evidence Downs and Black quality score: **16/27** Overall quality assessment: **Moderate**	Prospective cohort	**N: 304** No patients were reported as being lost to follow-up. Varying numbers of valid quality of life questionnaires are reported at each time point. **LDR**BT n 56 Age, years 67.5±5.9 PSA, ng/mL 6.4±1.5 Gleason score 5.7±0.6 Stage, n (%): T1 50 (89.3) T2 6 (10.7) Tx 0 (0) Risk category, n (%): Low 55 (98.2) Intermediate 1 (1.8) High 0 (0)	**Intervention:** ^{125}I LDRBT (without EBRT) to 144 Gy to the reference isodose (100%) as recommended by TG43 **Comparators:** External beam 3D conformal radiotherapy to a mean dose of 74.4 Gy (SD 4.2) RP with nerve sparing used in low-risk patients when feasible.	**Safety** Expanded Prostate Cancer Index Composite (EPIC) urinary, bowel, sexual and hormonal function Medical Outcomes Study 36-Item Short Form (SF-36) physical and mental component summaries (PCS and MCS)	24 months

Author & year, location and accrual period	Level of evidence and quality assessment	Study design	Study population (inclusion/exclusion criteria)	Intervention	Outcomes assessed (relevant to this review)	Duration of follow-up
			Neoadjuvant hormones, (%) 11 (19.7) RP / EBRT n 114 / 143 Age, years 63.9 (5.8) / 68.8 (5.7) PSA, ng/mL 7.9±3.3 / 11.9±9.2 Gleason score 6.3±0.8 / 6.4±1 Stage, n (%): T1 74 (64.9) / 56 (41.8) T2 40 (35.1) / 76 (56.7) Tx 0 (0) / 2 (1.5) Risk category, n (%): Low 49 (43) / 34 (25.4) Intermediate 60 (52.6) / 63 (47) High 5 (4.4) / 37 (27.6) Neoadjuvant hormones, n (%) 6 (5.3) / 53 (39.6) Risk definitions: Low = T1c or T2a and PSA ≤ 10 and Gleason ≤ 6 Intermediate = low risk but with T2b, or PSA = 11–20 or Gleason = 7 High = any of T2c or PSA > 20 or Gleason 8–10 Values are mean±SD unless otherwise specified.			
(Wei et al 2002) Single centre, US Accrual: June 1995	Level III-2 interventional evidence Downs and Black	Retrospective cohort	**N: 1,014** including 142 male controls who are not further considered‡ LDRBT	**Intervention:** BT performed via transperineal route with TRUS guidance at	**Safety** <u>Urinary, Bowel and Sexual Function</u> Summary scores from the EPIC* questionnaire were reported for urinary irritation, urinary	Median, 2 years

Author & year, location and accrual period	Level of evidence and quality assessment	Study design	Study population (inclusion/exclusion criteria)	Intervention	Outcomes assessed (relevant to this review)	Duration of follow-up
– May 1999	quality score: **16/27** Overall quality assessment: **Moderate**		n 112 Response rate, % 73.7 Age, years 67.2±7.3 Time since primary therapy, months 21 Adjuvant/neoadjuvant therapy, % 51 PSA, ng/mL 9.7±14.9 Gleason score, %: 2–6 68.3 7 59.5 8–10 4.8 Clinical stage, %: T1 35.7 T2 59.5 T3 4.8 EBRT / RP n 203 / 896 Response rate, % 72.4 / 74.9 Age, years 70.9±7.2 / 63.5±7.8 Time since primary therapy, months 29 / 30 Adjuvant/neoadjuvant therapy, % 33 / 28 PSA, ng/mL 9.1±12.7 / 7.3±7.2 Gleason score, %: 2–6 43.1 / 59.6 7 47.9 / 37.3 8–10 9.0 / 3.1 Clinical stage, %: T1 35.8 / 62.2	prescribed dose of 160 Gy A subset of patients (unknown proportion) received 80 Gy dosage and adjuvant EBRT **Comparators:** Retropubic RP EBRT using 3D conformal technique, delivered in 1.8–2.0 Gy daily fractions (5 days/week) to a prescribed dose of 55–80 Gy	incontinence, bowel and sexual function for follow-up exceeding 1 year General HRQoL FACT-P† component subscale scores were reported for follow-up exceeding one year * Expanded Prostate Index Composite † Functional Assessment of Cancer Therapy (prostate component)	

Author & year, location and accrual period	Level of evidence and quality assessment	Study design	Study population (inclusion/exclusion criteria)	Intervention	Outcomes assessed (relevant to this review)	Duration of follow-up
			T2 57.1 37.4 T3 7.1 0.4 Values are median±SD, except where indicated. ‡ A control group used in the primary analysis were not considered, given a secondary analysis made direct comparison between treatment modalities, in accordance with inclusion criteria for this assessment.			
(Kirschner-Hermanns et al 2008) Single institution, Germany Accrual: January 1999 – December 2002	Level III-2 interventional evidence Downs and Black quality score: **15/27** Overall quality assessment: **Poor**	Prospective cohort	**N: 94** (33 LDRBT, 61 RP patients) LDRBT eligibility: T1–T2a, PSA ≤ 10 ng/mL Gleason ≤ 6, prostate volume < 60 mL and no substantial residual urine No eligibility for RP group was provided. RP Age, years† 64 (54–75) PSA, ng/mL† 9.2 (1.6–55.6) Gleason score† 5 (3–8) Clinical stage, %: T1 35 T2 60 T3 5 OCO* 0.78 (0.08–2.67) Max flow < 10 mL/s, % 30 Residual vol > 50 mL, % 34# Max capacity < 200 mL, % 15 LDRBT Age, years† 67 (57–75)	**Intervention:** ^{125}I LDRBT with intraoperatively planned implant technique, prescribed to 145 Gy to cover the prostate plus 3–5 mm margin (except no margin posteriorly) D1 and D30 to the urethra were restricted to 250 Gy and 220 Gy respectively. Dose to 10% of the anterior rectal wall was restricted to < 145 Gy. Post-operative dosimetry was performed at 30 days following implant. **Comparator:** Perineal RP was performed using the extrasphincteric Young	**Safety** Urinary Function Urinary symptoms at 1 year following treatment Lower urinary tract symptoms (LUTS), urgency, incontinence, stress incontinence, having to wear pads and the bother associated with the above symptoms General HRQoL In addition, emotional functioning and global HRQoL (both using EORTC QLQ-C30) were assessed.	1 year

Author & year, location and accrual period	Level of evidence and quality assessment	Study design	Study population (inclusion/exclusion criteria)	Intervention	Outcomes assessed (relevant to this review)	Duration of follow-up
			PSA, ng/mL† 7.7 (3.2–17.0) Gleason score† 5 (2–7) Clinical stage, %: T1 36 T2 64 T3 0 OCO* 0.74 (0.34–1.70) Max flow < 10 mL/s, % 21 Residual vol > 50 mL, % 12# Max capacity < 200 mL, % 6 † Median (range) * Obstruction coefficient # Chi square, p=0.019 (RP cf LDRBT)	approach, with wide excision of the bladder neck and neurovascular bundles. No patients received adjuvant hormone therapy.		
(Kohan et al 2000) Single centre, US Accrual: June 1995 – September 1996	Level III-2 interventional evidence Downs and Black quality score: **15/27** Overall quality assessment: **Poor**	Prospective cohort	**N: 60** consecutive men with clinically localised prostate cancer (T1–T2, N0, M0) underwent RP (38) and LDRBT with ^{125}I (13) or ^{103}Pd (9) RP / LDRBT Age, years 61.2 (43–71) / 71.1 (60–86) Clinical stage, n (%): T1 18 (47.4) / 7 (31.8) T2 20 (52.6) / 15 (68.2) PSA, ng/mL 8.4 (2.2–34) / 12 (2.3–37.7) Gleason score 6 (4–8) / 6 (4–8)	**Intervention**: LDRBT **Comparator**: RP	**Cost** (1-year charge comparison) Hospital and outpatient records were used to compare pre-operative, operative and post-operative charges for LDRBT and RP patients based on diagnosis-related group indexed against ICD-9 code.	NA
(Tsui et al 2005) Single institution, Canada	Level III-2 interventional evidence Downs and Black	Retrospective cohort	**N: 202** All patients were treated 1998–2002 with either LDRBT or EBRT with T1 or T2 prostate	**Intervention:** Two-stage (pre-operative planning) ^{125}I LDRBT, prescribed to	**Safety** <u>Urinary, bowel and sexual function</u> Data collected for brachytherapy patients and	Median (range), months LDRBT:

Author & year, location and accrual period	Level of evidence and quality assessment	Study design	Study population (inclusion/exclusion criteria)	Intervention	Outcomes assessed (relevant to this review)	Duration of follow-up
Accrual: 1998–2000	quality score: **15/27** Overall quality assessment: **Poor**		cancer, PSA < 20.0 ng/mL and Gleason ≤ 8. 28 records had incomplete data and 10 records were unavailable at the time of the study, leaving 76 EBRT and 86 LDRBT patients for analysis. LDRBT / RT Age, years: 64.8±6.5 / 66.3±5.1 Stage, n (%)†: T1c: 50 (63.3) / 35 (47.9) T2a: 28 (35.4) / 21 (28.8) T2b: 1 (1.3) / 16 (21.9) T2c: 0 (0) / 1 (1.4) PSA, ng/mL: 6.2±2.3 / 9.1±3.7 Gleason score n (%)†: ≤ 6: 83 (97.6) / 30 (40.5) 7: 2 (2.4) / 41 (55.4) 8: 0 (0) / 3 (4.1) Urinary symptoms, %: Inc. frequency: 64.5 / 13.5† Urgency: 35 / 9.6‡ Weak stream: 45.9 / 26.9 Nocturia: 85.5 / 46.2† TURP, n (%): 3.5 / 9.2 α-blocker, %: 3.5 / 6.6 Neoadjuvant ADT,%: 32.9 / 13.2* Values are mean±SD unless otherwise specified. Fisher's exact is for categorical variables, two sample t-test for normally distributed variables	145 Gy (TG43) All patients were discharged without a catheter and with an alpha blocker for a minimum of 3 months. **Comparator:** 18 MV photon 3D-CRT prescribed to 75.6 Gy in 1.8 Gy fractions using a six-field coplanar technique Three gold seed fiducials were inserted before planning. The prostate was planned with a margin of 7 mm posteriorly (at the rectal interface) and 10 mm elsewhere.	radiotherapy patients differed BT patients: IPSS (self reported), clinician description of bowel and sexual function, use of medications for symptom management 3D-CRT patients: RTOG late radiation morbidity scores, clinician description of sexual function and use of medications Urinary, sexual and bowel symptoms were reported at 6, 12, 18, 24, 30, 36 and 42 months after (the beginning of) treatment. The different scores are not comparable and have not been presented. Statistical comparisons were not possible and not performed by the authors.	45 (18–63) RT: 62 (18–79)

Author & year, location and accrual period	Level of evidence and quality assessment	Study design	Study population (inclusion/exclusion criteria)	Intervention	Outcomes assessed (relevant to this review)	Duration of follow-up
			and Wilcoxon rank sum tests for variables with non-normal distributions. Stage data were only available for 79 and 73 LDRBT and EBRT patients, respectively, while Gleason scores were obtained only for 85 and 74 of these patients. † p<0.001, * p=0.005, ‡ p=0.009			
(Wyler et al 2009) Single centre, Switzerland Accrual: LDRBT patients, March 2001 – December 2004 EBRT patients, January 2002 – December 2004	Level III-2 interventional evidence Downs and Black quality score: **14/27** Overall quality assessment: **Poor**	Retrospective cohort	**N: 212** consecutive patients with clinically localised prostate cancer **LDR**BT / RP n: 70 / 142 Age, years (range): 61 (49–75) / 64 (47–75) PSA, ng/mL: 6.1 (1.1–12.8) / 11.3 (0.3–24) Gleason score: 5.7 (4–7) / 6.3 (5–9) Clinical risk*, n: Low: 39 / 27 Intermediate: 16 / 24 High: 0 / 54 * Clinical risk was low (PSA < 10 ng/mL, stage T1c–T2a and Gleason score < 7), intermediate (PSA 10–20 ng/mL or stage T2b or Gleason score = 7) or high (not defined). Only patients with prostate volume < 60 mL and urinary flow rate > 10 mL/s were selected. 79% of LDRBT patients and 74% of RP patients returned questionnaires.	**Intervention**: LDRBT with prescription dose of 145 Gy using real-time planning; 0.3 cm^3 of the rectal wall received the target dose of 145 Gy. **Comparator**: RP (nerve sparing in select cases of pre-operatively potent patients)	**Safety** Urinary, bowel and sexual function HRQoL questionnaires* assessed urinary and bowel function, however, no analysable data specific to urinary function were provided * European Organization for Research and Treatment Quality of Life Questionnaire (EORTC-QLQ-C30), International Prostate Symptom Score (IPSS) and International Index of Erectile Function (IIEF-5) General HRQoL General QoL, including pain (not defined specifically as urinary, bowel or sexual in origin) was also measured using EORTC-QLQ surveys.	Mean, months LDRBT: 28 RP: 20

Author & year, location and accrual period	Level of evidence and quality assessment	Study design	Study population (inclusion/exclusion criteria)	Intervention	Outcomes assessed (relevant to this review)	Duration of follow-up
(Vicini et al 2002) Multicentre, US and Germany Accrual: 1989–1998	Level III-3 interventional evidence Downs and Black quality score: **12/27** Overall quality assessment: **Poor**	Comparison of two matched single arms	**N: 6,877** men with prostate cancer, of whom 5,179 are not considered for this analysis*, leaving data for 1,698 patients LDRBT (Centre 1) / (Centre 2) n: 207 / 330 Age, years: 73 / 69 Follow-up, months: 62 / 78 PSA, ng/mL: 6 / 6 Gleason score: NR† / 5 3D-EBRT (Centre 3) / EBRT (Centre 4) n: 357 / 313 Age, years: 68 / 73 Follow-up, months: 46 / 51 PSA, ng/mL: 6 / 6 Gleason score: 6 / 6 RP (Centre 5) n: 491 Age, years: 61 Follow-up, months: 34 PSA, ng/mL: 6 Gleason	**Intervention:** LDRBT; radioactive source or further treatment details not specified **Comparators:** (3D)-EBRT (dosed at a range of 66–73 Gy) and RP (treatment details unspecified)	**Effectiveness** Five-year biochemical-free recurrence Five-year overall survival	Median, 36 months

Author & year, location and accrual period	Level of evidence and quality assessment	Study design	Study population (inclusion/exclusion criteria)	Intervention	Outcomes assessed (relevant to this review)	Duration of follow-up
			score 6 Loss to follow-up: None evident in any patient group/centre. Values are median, except where specified. * These patients had one or more of the following: PSA > 10 ng/L, Gleason score > 7, clinical stage T3, an ineligible treatment (high density radiotherapy, neutron therapy). † Not reported. Reporting of Gleason score was at the discretion of each participating centre; although no median score is available, this data was presented in a table for patients with a score ≤ 6.			
(Pinkawa et al 2009) Single centre, Germany Accrual: 2003–2006	Level III-3 interventional evidence Downs and Black quality score: **16/27** Overall quality assessment: **Moderate**	Comparison of two matched single arms LDRBT and EBRT patients, matched on age (±5 years, prostate volume ±10 cc, use of ADT and erectile function (no ability to have an erection, poor ability to have an erection, erection sufficient for sexual intercourse)	**N: 104** (52 in each group) LDRBT / EBRT Age, years: 68 (51–77) / 68 (48–77) Prostate volume: 37 (18–60) / 35 (22–68) PSA, ng/mL: 7 (1.5–14) / 8 (2.5–24) Neo-ADT: 14 (27) / 14 (27) Gleason score < 7: 50 (96) / 39 (75) T-stage ≤ 2a: 51 (98) / 43 (83) Comorbidities: 27 (52) / 25 (48) Comorbidities with incidence > 5%: Hypertension: 11 (21) / 11(21) CHD: 6 (12) / 13 (25) Diabetes: 6 (12) / 7 (14) COPD: 4 (8) / 6 (12) Values are median (range) or n (%).	**Intervention:** Intra-operative ^{125}I LDRBT performed under spinal or general anaesthesia, with 57±9 sources implanted with 22±8 needles, preferentially implanted in the periphery (no extra prostatic seeds planned), prescribed to 145 Gy **Comparator:** 3D conformal EBRT patients were planned and treated with a full bladder with a four-field technique using 15 MeV photons, anterior/lateral margins of 1.5 cm, and	**Safety** <u>Urinary, bowel and sexual function</u> Expanded Prostate Cancer Index Composite (EPIC) questionnaire given to patients at or before treatment (time A), 1 month after LDRBT or at the last day of EBRT (time B) and a median time of 16 months following treatment (time C). Specific outcomes are: urinary bother, bowel bother, incontinence, pad usage, problem of dripping urine or painful urination, bloody stools, painful bowel movements, problem from increased frequency of bowel movements, sexual function score. Scores at times A, B and C, and the change in score between times A and B, and times A and C are compared for EBRT and LDRBT.	Median, months 16 Range BT: 12–24 EBRT: 12–21

Author & year, location and accrual period	Level of evidence and quality assessment	Study design	Study population (inclusion/exclusion criteria)	Intervention	Outcomes assessed (relevant to this review)	Duration of follow-up
			LDRBT post implant dosimetry at 1 month, (mean±SD) D90, Gy 152±26 V100, % 91±6% V150, % 65±13% Urethra D30, Gy 207±30 Urethra D10, Gy 238±67 Rectum D2 cc, Gy 114±37 Rectum D0.1 cc, Gy 224±80	craniocaudal and dorsal margins of 1 cm Treatment was planned to 70.2–72.0 Gy in 1.8–2.0 Gy fractions.		
(Ollendorf et al 2009a) Health technology assessment US Patient accrual is varied (HTA is based on three separate systematic reviews). Included studies were published during January 1996 – May 2009 for RP and AS, 1995 – August 2008 for IMRT, and 1995 – August 2008 for LDRBT (the LDRBT systematic review also updated the IMRT review).	Level of evidence for this HTA cannot be assessed. The systematic reviews on which the HTA is based rely primarily on non-comparative evidence (level IV) Quality: good (Drummond & Jefferson 1996)	Health technology assessment (HTA)	**Adverse event rates** The HTA used adverse event rates from systematic reviews, which required included studies to contain 'a preponderance' of patients of clinical stage T1–T2a, Gleason score ≤ 6 and PSA < 10 ng/mL. However, studies including intermediate risk patients were not excluded. Baseline adverse event rates were taken from Bacon et al (2003) and Andersson et al (2004) **Patient utilities** Stewart et al (2005) Dale et al (2008); Sullivan & Ghushchyan (2006) **Transition probabilities** D'Amico et al (1999); Alibhai et al (2003); Horwitz et al (2005) **Costs** US Medicare and other sources	**Cost–utility analysis comparing:** RP EBRT (specifically IMRT) LDRBT AS	**Modelled economic analysis: cost–utility** Incremental cost, incremental QALY, incremental cost-effectiveness ratio (cost per QALY)	N/A

Author & year, location and accrual period	Level of evidence and quality assessment	Study design	Study population (inclusion/exclusion criteria)	Intervention	Outcomes assessed (relevant to this review)	Duration of follow-up

Table notes:
3D-CRT = three-dimensional conformal radiotherapy (a type of EBRT); ADT = androgen deprivation therapy; AS = active surveillance; bNED = biochemical no evidence of disease (freedom from biochemical recurrence); LDRBT = low-dose-rate brachytherapy; CT= computerised tomography; D90 = the dose delivered to 90% of the planned radiotherapy target; EBRT = external beam radiotherapy; EORTC = European Organisation for Research and Treatment of Cancer; EORTC QLQ-C30 = EORTC quality of life questionnaire – cancer; EORTC QLQ-PR25 = EORTC quality of life questionnaire - prostate cancer module; EPIC = Expanded Prostate cancer Index Composite; FACT-P = Functional Assessment of Cancer Therapy - Prostate module; HRQoL = health-related quality of life; HTA = health technology assessment; ICER = incremental cost effectiveness ratio; IIEF = International Index of Erectile Function; IMRT = intensity modulated radiotherapy; IPSS = International Prostate Symptom Score; LHRHa = luteinising hormone releasing hormone analogue; PSA = prostate specific antigen; QALY = quality adjusted life year; RP = radical prostatectomy; RTOG = Radiation Therapy Oncology Group; SF-36 = Short Form–36 health survey; UCLA-PCI = University of California, Los Angeles - Prostate Cancer Index; V100 = the volume of the planned radiotherapy target that received 100% of the prescribed dose

Study profiles of included case series

Author & year, location and accrual period	Level of evidence and quality assessment	Study design	Study population (Inclusion/exclusion criteria)	Intervention	Outcomes assessed (relevant to this review)	Duration of follow-up
(Bucci et al 2002) Single centre, Canada Accrual: June 1998 – August 2000	Case series Level IV interventional evidence NHMRC case series quality score: **6/6** Overall quality assessment: **Good**	Case series	**N: 282** Age, years Median 66 (38–78) Clinical stage T1c-T2b Gleason score ≤ 7 (3+4 only) PSA: ≤ 10 ng/mL 82% 10 - ≤ 15 ng/mL 18%	LDRBT dosed to 144 Gy as per TG-43 protocol.	Rate of urinary obstruction requiring catheterisation	Median = 12 months
(Crook et al 2008) Single centre, Canada Accrual: March 1999 – July 2005	Case series Level IV interventional evidence NHMRC case series quality score: **6/6** Overall quality assessment: **Good**	Case series	**N: 484** Age, years Mean 63.1 (SD±6.9) Clinical stage T1c–T2a Gleason score ≤ 6 PSA ≤ 10 ng/mL	^{125}I LDRBT D90 = 160.6 Gy	Increase obstructive or irritative symptoms (IPSS) from baseline Rates of urinary urgency Rates of urinary retention, urethral stricture and catheterisation after 1 year following treatment	Median = 41 months
(Sacco et al 2003) Single centre, Israel Accrual: September 1996 – October 2001	Case series Level IV interventional evidence NHMRC case series quality score: **6/6** Overall quality assessment: **Good**	Case series	**N: 400** consecutive patients with early stage prostate cancer Age, years Median (range) = 65 (41–70) Clinical stage T1c: 73%, >T2a: 27% Gleason score 98% of patients ≤ 7 PSA 91% of patients ≤ 10 ng/mL	LDRBT with a prescribed dose of either 145 Gy or 115 Gy, depending on whether iodine or palladium seeds were used—324 (82%) and 73 (18%) of patients respectively. 52 (13%) patients received EBRT in addition to LDRBT	Number of patients who developed acute urinary retention requiring catheterisation Median number of days to development of acute urinary retention requiring catheterisation Median (range) duration of catheterisation, days Proportion of patients with acute urinary retention among those who did and did not use corticosteroids (dexamethasone) Number of patients with gross haematuria	Median = 2.1 years
(Keyes et al 2009)	Case series	Case series	**N: 712** eligible from 932 consecutive patients	^{125}I LDRBT prescribed	IPSS flare following treatment with LDRBT	Median =

Multicentre, Canada. Accrual: July 1998 – June 2003	Level IV interventional evidence NHMRC case series quality score: **5/6** Overall quality assessment: **Good**		Age Median 65.5 (46–82) years Clinical stage <T2c Gleason score ≤ 7 PSA, ng/mL: ≤ 10 85.8% 10 – ≤ 15 14.2% Follow-up at least 34 months: 144 excluded due to living in remote area, 35 less than 34 months follow-up, 41 with insufficient data.	to a dose of 144 Gy (TG-43) to cover ≥ 98% of the planning target volume (1–5 mm margins).	Late RTOG urinary and bowel toxicity Erectile function	57.1 months
(Mabjeesh et al 2007) Single centre, Israel Accrual: June 1998 – June 2006	Case series Level IV interventional evidence NHMRC case series quality score: **5/6** Overall quality assessment: **Good**	Case series	**N: 655** men with localised prostate cancer Age, years Mean±SD = 67.3±6.5 Clinical stage T1–T2c Gleason score 99.9% of patients ≤ 7 PSA, ng/mL Mean±SD = 7.75±3.45 Loss to follow-up: None apparent.	LDRBT using either pre-planning or real-time techniques	Number of patients with urinary retention requiring catheterisation Median time to onset of urinary retention requiring catheterisation Median duration of catheterisation Number of patients with urethral stricture	Mean = 45 months
(Matzkin et al 2003) Single centre, Israel Accrual: not reported	Case series Level IV interventional evidence NHMRC case series quality score: **5/6** Overall quality assessment: **Good**	Case series	**N:300** Group 1: 136 pre-planned Group 2: 164 intraoperatively planned Age, years: G1: Mean 67.2 G2: Mean 68.4 Clinical stage ≤ T2 Gleason score ≤ 6 PSA: G1: Mean 8.69	**^{125}I** LDRBT monotherapy prescribed to a dose of 145 Gy if pre-planned, or 160 Gy if planned intraoperatively, according to TG-43 recommendations.	Urinary symptoms and IPSS following implantation	Analyses were limited to 24 months follow-up.

			G2: Mean 7.95			
(Mitchell et al 2008) Multicentre, UK Accrual: January 2003 – October 2006	Case series Level IV interventional evidence NHMRC case series quality score: **5/6** Overall quality assessment: **Good**	Case series	**N: 1,535** men treated with permanent seed LDRBT Age, median, years (range): Centre 1: 63 (43–79) Centre 2: 65 (40–79) Centre 3: 63 (43–82) Clinical stage T1c–T3a Gleason score > 97% of patients ≤ 7 PSA, ng/mL ≤ 7 Loss to follow-up: NA, complete reporting for all patients registered on database.	LDRBT with pre-plan D90 range of 179–189 Gy	IPSS* at baseline, 6 weeks and 12 months following implant Median duration of catheterisation Urethral stricture rates *International Prostate Symptom Score	Median = 21 months
(Stone et al 2010) Single centre, US Accrual: 1990–2006	Case series Level IV interventional evidence NHMRC case series quality score: **5/6** Overall quality assessment: **Good**	Case series	**N: 395** Age, years Mean 68.9 (SD±6.8) Clinical stage T1b–T3a Gleason score ≤ 7 98.2% PSA, ng/mL: ≤ 10 83.3% 10 – ≤ 20 14.4% > 20 2.3% Prostate volume > 50 cc 85% of men treated with ^{125}I LDRBT	**^{125}I** (n=335) or ^{103}Pd (n=60) LDRBT monotherapy. 52% received androgen deprivation therapy for 3 months **before** implantation. **^{125}I** LDRBT was prescribed to a dose of 160 Gy (TG-43).	Rates of urinary retention *Note: may have overlapping population with Kao 2007.*	Median = 6 years
(Zelefsky et al 2007a) Single centre, US Accrual: January 1998 – December 2004	Case series Level IV interventional evidence NHMRC case series quality score: **5/6** Overall quality	Case series	**N:562** Age Not reported Clinical stage 99.8% ≤ T2 Gleason score 99.8% ≤ 7	^{125}I LDRBT monotherapy prescribed to a dose of 144 Gy	Incidence of late Grade 2 and 3 NCI CTCAE rectal and urinary side effects.	Median = 40 months

	assessment: **Good**		PSA, ng/mL: ≤ 10 94.5% 10 – ≤ 20 5.3% > 20 0.2%			
(Kao et al 2008) Single centre, US Accrual: June 1995 – February 2005	Case series Level IV interventional evidence NHMRC case series quality score: **4/6** Overall quality assessment: **Moderate**	Case series	**N: 643** men with localised prostate cancer Age Not reported Clinical stage T1a– T2c Gleason score 98.8% of patients ≤ 7 PSA Median = 6.1 ng/mL Loss to follow-up: Urinary outcomes were available for 249 patients. Erectile function data were available for 572 men, of whom 420 were potent and assessed following treatment. Patient numbers available for bowel outcomes unclear.	LDRBT with D90 > 180 Gy, median = 197 Gy (range, 180–267 Gy) via real-time planning	Change in median IPSS* from baseline Acute urinary retention Patient-reported urinary QoL (undefined scale) Freedom from Grade 2 or higher rectal bleeding at 3 and 5 years (as per National Cancer Institute Common Terminology Criteria for Adverse Events) Physician-assessed erectile function (among subjects potent before LDRBT procedure) * International Prostate Symptom Score	Median = 4.5 years
(MacDonald et al 2005) Single centre, Canada Accrual: July 1998 – January 2002	Case series Level IV interventional evidence NHMRC case series quality score: **4/6** Overall quality assessment: **Moderate**	Case series	**N: 342 men potent at baseline** Age Median = 65 (49–80) years Clinical stage ≤ T2 Gleason score ≤ 7 PSA Mean = 6.7 (SD±3.3) ng/mL Prostate volume < 50 cc	**^{125}I** LDRBT monotherapy prescribed to a dose of 144 Gy to > 99% of the planning target volume (0.5–1.0 cm margin superiorly and inferiorly).	Physician and patient document rates of erectile dysfunction at 1–3 years following implantation.	Follow-up not reported
(Eckman et al 2010) Single centre, US Accrual: 1995–2007	Case series Level IV interventional evidence NHMRC case series quality score: **3/6**	Case series	**N: 394** Age Mean = 67.3 (SD±7.6) years Clinical stage 99.5% < T3 Gleason score	**^{125}I** LDRBT monotherapy prescribed to a dose of 145 Gy	Rates of urinary retention requiring catheterisation Rates of urinary symptoms (frequency, hesitancy, urgency, decreased force, haematuria, nocturia, dysuria and use of medication for urinary symptoms) among men without symptoms at baseline	Mean = 5 years

	Overall quality assessment: **Moderate**		95.7% < 8 PSA Mean = 7.7 (SD±4.7) ng/mL 2.8% received adjuvant EBRT.		Rates of bowel symptoms (diarrhoea, constipation, rectal bleeding, pain with defecation and use of medication for bowel symptoms) among men without symptoms at baseline Rates of impaired potency, blood in the semen, painful ejaculations and use of medication for erectile dysfunction in men who did not report these symptoms at baseline	
(Elshaikh et al 2003) Single centre, US Accrual: 1996–2001	Case series Level IV interventional evidence NHMRC case series quality score: **3/6** Overall quality assessment: **Moderate**	Case series	**N: 402** Age Median = 69 years Clinical stage ≤ T2 Gleason score Median 6 (4–8) PSA Median = 6.45 ng/mL	**^{125}I** LDRBT monotherapy prescribed to a dose of 144 Gy according to American Brachytherapy Society recommendations	Rates of intermittent self-catheterisation for urinary retention following implantation	Follow-up not recorded
(Schafer et al 2008) Single centre, Germany Accrual: June 1998 – December 2003	Case series Level IV interventional evidence NHMRC case series quality score: **2/6** Overall quality assessment: **Poor**	Case series	**N: 258** (296 treated consecutively, 38 patients died before assessment) Age Median = 71 years Clinical stage 94% ≤ T2 Gleason score: ≤ 7 71% ≥ 8 0.4% Unknown 28.6% PSA Median = 7.3 ng/mL	**^{125}I** LDRBT monotherapy prescribed to a minimum peripheral dose > 140 Gy (TG-43).	Pad usage following implantation Faecal incontinence or bloody stools following implantation Questionnaires were sent out to all patients simultaneously, at between 13 and 78 months following implantation (median = 51 months).	Median = 51 months

Table notes:
LDRBT = low-dose-rate brachytherapy; IIEF = International Index of Erectile Function; IMRT = intensity modulated radiotherapy; IPSS = International Prostate Symptom Score; LHRHa = luteinising hormone releasing hormone analogue; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PSA = prostate specific antigen; RTOG = Radiation Therapy Oncology Group

Appendix K Other eligible case series

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Appendix L Excluded studies

Incorrect population

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Appendix M Unit costs for treating localised prostate cancer

Table 37 Unit costs of services and medications relating to low-dose-rate ^{125}I brachytherapy for localised prostate cancer over a 12-month period

Component	Description	Cost (full fee)	Source of estimate	Rationale and assumptions
Initial urologist consult	SPECIALIST, REFERRED CONSULTATION – SURGERY OR HOSPITAL (Professional attendance at consulting rooms or hospital by a specialist in the practice of his or her specialty where the patient is referred to him or her) – INITIAL attendance in a single course of treatment, not being a service to which ophthalmology items 106, 109 or obstetric item 16401 apply	$80.85	MBS item 104	Regardless of final treatment decision, men will be seen initially by a urologist.
Initial radiation oncologist consult	As above	$80.85	MBS item 104	
Urine flow study	URINE FLOW STUDY including peak urine flow measurement, not being a service associated with a service to which item 11919 applies	$26.05	MBS item 11900	Over a 20-month period, almost as many patients receiving 15338 also received a urine flow study. It is likely that this will be part of a routine work-up for patients receiving brachytherapy.
Whole-body radionuclide scan	BONE STUDY – whole body, with, when undertaken, blood flow, blood pool and delayed imaging on a separate occasion (R)	$479.80	MBS item 61421	Over a 20-month period[a], 62% of patients who received 15338 also incurred a WBBS item number—either 61421 (76%) or 61425 (24%).
Computed tomography scan	COMPUTED TOMOGRAPHY – scan of upper abdomen and pelvis with intravenous contrast medium and with any scans of upper abdomen and pelvis before intravenous contrast injection, when undertaken, not for the purposes of virtual colonoscopy, not being a service to which item 56807 or 57007 applies (R) (K) (Anaes.)	$480.05	MBS item 56507	Over a 20-month period[a], computerised tomography is likely to have been used on close to 100% of men, with 56507 and 56409 occurring equally as often.
	COMPUTED TOMOGRAPHY – scan of pelvis only (iliac crest to pubic symphysis) without intravenous contrast medium not being a service associated with a service to which item 56401 applies (R) (K) (Anaes.)	$250.00	MBS item 56409	
	Mean cost of computed tomography	$365.03	(56507 + 56409) / 2	

Component	Description	Cost (full fee)	Source of estimate	Rationale and assumptions
Pre-anaesthetic consult	ANAESTHETIST, PRE-ANAESTHESIA CONSULTATION (Professional attendance by a medical practitioner in the practice of ANAESTHESIA) – a BRIEF consultation involving a targeted history and limited examination (including the cardio-respiratory system) – AND of not more than 15 minutes duration, not being a service associated with a service to which items 2801–3000 apply	$40.60	MBS item 17610	
Brachytherapy planning	BRACHYTHERAPY PLANNING, computerised radiation dosimetry for ^{125}I seed implantation of localised prostate cancer, in association with item 15338	$592.90	MBS item 15539	
Brachytherapy implant (urologist component)	PROSTATE, radioactive seed implantation of, urological component, using transrectal ultrasound guidance, for localised prostatic malignancy at clinical stages T1 (clinically inapparent tumour not palpable or visible by imaging) or T2 (tumour confined within prostate), with a Gleason score of less than or equal to 7 and a prostate specific antigen (PSA) of less than or equal to 10 ng/mL at the time of diagnosis. The procedure must be performed by a urologist at an approved site in association with a radiation oncologist, and be associated with a service to which item 55603 applies.	$986.90	MBS item 37220	
Brachytherapy implant (radiation oncologist component)	PROSTATE, radioactive seed implantation of, radiation oncology component, using transrectal ultrasound guidance, for localised prostatic malignancy at clinical stages T1 (clinically inapparent tumour not palpable or visible by imaging) or T2 (tumour confined within prostate), with a Gleason score of less than or equal to 7 and a prostate specific antigen (PSA) of less than or equal to 10 ng/mL at the time of diagnosis. The procedure must be performed at an approved site in association with a urologist.	$884.25	MBS item 15338	

Component	Description	Cost (full fee)	Source of estimate	Rationale and assumptions
Transrectal ultrasound	PROSTATE, bladder base and urethra, transrectal ultrasound scan of, where performed: (a) personally by a medical practitioner who undertook the assessment referred to in (c) using a transducer probe or probes that: (i) have a nominal frequency of 7–7.5 megahertz or a nominal frequency range which includes frequencies of 7–7.5 megahertz; and (ii) can obtain both axial and sagittal scans in 2 planes at right angles; and (b) following a digital rectal examination of the prostate by that medical practitioner; and (c) on a patient who has been assessed by a specialist in urology, radiation oncology or medical oncology or a consultant physician in medical oncology who has: (i) examined the patient in the 60 days before the scan; and (ii) recommended the scan for the management of the patient's current prostatic disease (R).	$109.10	MBS item 55603	A transrectal ultrasound is required during the brachytherapy procedure to localise seed placement.
Anaesthesia	INITIATION OF MANAGEMENT OF ANAESTHESIA for brachytherapy using radioactive sealed sources	$93.50	MBS item 21973	Based on a procedure time of between 76 and 90 minutes *Note: item 23063 was not identified as a fee associated with brachytherapy over a 20-month period.
	1:26 HOURS TO 1:30 HOURS	$112.20	MBS item 23063	
Intra-operative imaging	FLUOROSCOPY using a mobile image intensifier, in conjunction with a surgical procedure lasting 1 hour or more, not being a service associated with a service to which another item in this table applies (R)	$98.90	MBS item 60509	Over a 20-month period, these two items combined were present about two-thirds of the time. This procedure is likely associated with intra-operative planning. They were used roughly equally as often.
	FLUOROSCOPY using a mobile image intensifier, in conjunction with a surgical procedure lasting less than 1 hour, not being a service associated with a service to which another item in this table applies (R)	$63.75	MBS item 60506	
	Mean cost of fluoroscopy (per patient based on item usage in two-thirds of cases)	$54.21	(60509 + 60506) / 2 * 2/3	

Component	Description	Cost (full fee)	Source of estimate	Rationale and assumptions
Post-implant dosimetry	RADIATION SOURCE LOCALISATION using a simulator or x-ray machine or CT of a single area, where views in more than 1 plane are required, for brachytherapy planning for ^{125}I seed implantation of localised prostate cancer, in association with item 15338	$289.75	MBS item 15513	
Hospital costs	AR-DRG L08B – Urethral procedures-CC (private)	$1,577.00	NHCDC Cost Report Round 13	70% occur in private and 30% occur in public hospitals. Private cost has been adopted for public hospitals, and wages for radiation oncologists, urologists and anaesthetists are assumed to be that of the MBS fee.
^{125}I brachytherapy seeds	Pre-loaded, stranded ^{125}I seeds	$7,000.00	Prostheses List code ON003	Listed benefit ranges from $6,800 to $7,150, depending upon prescription; $,7000 is taken as an approximation.
Luteinising hormone releasing hormone analogue	GOSERELIN ACETATE Subcutaneous implant (long acting) 10.8 mg (base) in pre-filled injection syringe	$1,108.76	PBS code 8093Y	Assume usage in one-third of patients for 3 months prior.
	Mean cost per patient for LHRHa	$369.59	8093Y * 1 courses / 3 (one-third of patients)	

[a] Data from 1/9/2009 to 30/4/2010—the count of additional item numbers of men who received item 15338 in this period. The count will underestimate the actual usage of services as patients may have accessed services before the period or may still access services after the period that could reasonably be linked with the use of 15338. However, some services accessed over this time period will be unrelated to 15338. Expert opinion from the Advisory Panel suggests that whole-body radionuclide scan and computerised tomography scans are unnecessary in men with Gleason 6 (or less) disease and their use has only been costed for men with Gleason 7 prostate cancer. However, it is clear that a proportion of men with Gleason 6 disease do receive these pre-treatment staging scans and the overall estimation of cost associated with the treatment of Gleason 6 (or less) disease will therefore be underestimated.

Table 38 Unit costs of services and medications relating to radical external beam radiotherapy for localised prostate cancer over a 12-month period

Component	Description	Cost (full fee)	Source of estimate	Rationale and assumptions
Initial urologist consult	As brachytherapy Table 37 above	$80.85	MBS item 104	Regardless of final treatment decision, men will be seen initially by a urologist.
Initial Radiation Oncologist consult	As brachytherapy Table 37 above	$80.85	MBS item 104	
Whole-body radionuclide scan	As brachytherapy Table 37 above	$479.80	MBS item 61421	Assume the use of WBBS does not differ between treatments
Computed tomography scan	As brachytherapy Table 37 above Mean cost of computed tomography	$365.03	(56507 + 56409) / 2	Assume the use of CT does not differ between treatments
Radiotherapy simulation	SIMULATION FOR THREE DIMENSIONAL CONFORMAL RADIOTHERAPY without intravenous contrast medium, where: (a) treatment set-up and technique specifications are in preparations for three-dimensional conformal radiotherapy dose planning; and (b) patient set-up and immobilisation techniques are suitable for reliable CT image volume data acquisition and three dimensional conformal radiotherapy treatment; and (c) a high-quality CT-image volume dataset must be acquired for the relevant region of interest to be planned and treated; and (d) the image set must be suitable for the generation of quality digitally reconstructed radiographic images	$622.45	MBS item 15550	CT Simulation without contrast for 3D-CRT
Radiotherapy planning	DOSIMETRY FOR THREE DIMENSIONAL CONFORMAL RADIOTHERAPY OF LEVEL 3 COMPLEXITY - where: (a)* (b) dosimetry for a two-phase three-dimensional conformal treatment plan using CT image volume datasets with at least one gross tumour volume, and (i) two planning target volumes; or (ii) two organ at risk dose goals or constraints defined in the prescription. or (c)* (d)* * additional details can be accessed at MBS online	$1059.25	MBS item 15562	2 phase 3D-CRT with 2 organs at risk and 2 planning volumes

Component	Description	Cost (full fee)	Source of estimate	Rationale and assumptions
Daily imaging / verification	RADIATION ONCOLOGY TREATMENT VERIFICATION - multiple projection acquisition when prescribed and reviewed by a radiation oncologist and not associated with item 15700 or 15710 - each attendance at which treatment involving three or more fields is verified (ie maximum one per attendance).	$2834.20	MBS item 15705	$76.60 per fraction at 37 fractions
Treatment Delivery	RADIATION ONCOLOGY TREATMENT, using a dual photon energy linear accelerator with a minimum higher energy of at least 10MV photons, with electron facilities - each attendance at which treatment is given - 1 field - treatment delivered to primary site (prostate)	$2086.80	MBS item 15248	$56.40 per fraction for 37 fractions (initial field) $35.85 per fraction per extra field for 37 fractions assuming a 5 field technique
	RADIATION ONCOLOGY TREATMENT, using a dual photon energy linear accelerator with a minimum higher energy of at least 10MV photons, with electron facilities - each attendance at which treatment is given - 2 or more fields up to a maximum of 5 additional fields (rotational therapy being 3 fields) - treatment delivered to primary site (prostate)	$5305.80	MBS item 15263	
	Total cost of treatment delivery	$7392.60	15248 * 37 (fractions) + 15263 * 4 (fields) * 37 (fractions)	
Luteinising hormone releasing hormone analogue (Gleason 7 patients only – Expert opinion)[a]	GOSERELIN ACETATE Subcutaneous implant (long acting) 10.8 mg (base) in pre-filled injection syringe	$1108.76	PBS code 8093Y	Assume usage in 1/3 of Gleason 7 patients for 3 months before and 3 months after implantation
	Mean cost per patient for LHRHa	$739.17	8093Y * 2 courses / 3 (a third of patients)	

[a] Expert opinion from Advisory Panel members regard the use of LHRHa among men with Gleason 6 (or less) disease unnecessary. In addition, the use of LHRHa is deemed far less likely among men with Gleason 3+4=7 disease than among the higher risk patients with Gleason 4+3=7. Rather than create a separate subgroup for costing, LHRHa has been costed for all patients with Gleason 7 disease. Therefore, the cost of treating men with Gleason 3+4=7 will be an over-estimate of the true costs.

Table 39 Unit costs of services and medications relating to radical prostatectomy for localised prostate cancer over a 12-month period

Component	Description	Cost (full fee)	Source of estimate	Rationale and assumptions
Initial urologist consult	As brachytherapy Table 37 above	$80.85	MBS item 104	Regardless of final treatment decision, men will be seen initially by a urologist.
Whole-body radionuclide scan	As brachytherapy Table 37 above	$479.80	MBS item 61421	Assume the use of WBBS does not differ between treatments.
Computed tomography scan	As brachytherapy Table 37 above Mean cost of computed tomography	$365.03	(56507 + 56409) / 2	Assume the use of CT does not differ between treatments.
Pre-anaesthetic consult	As brachytherapy Table 37 above	$40.60	MBS item 17610	
Surgeon fee	PROSTATECTOMY, radical, involving total excision of the prostate, sparing of nerves around the bladder and bladder neck reconstruction, not being a service associated with a service to which item 35551, 36502 or 37375 applies	$1,505.95	MBS item 37210	Assume nerve sparing, assume no patient undergoes lymphadenectomy (low risk?).
Assistant surgeon fee	Assistance at any operation identified by the word 'Assist.' for which the fee exceeds $527.65 or at a series of operations identified by the word 'Assist.' for which the aggregate fee exceeds $527.65	$301.19	MBS item 51303	Assume assistant at all procedures.
Hospital costs	AR-DRG M01Z – Major male pelvic procedures (private)	$8,685	NHCDC Cost Report Round 13	74% occur in private and 26% occur in public hospitals.
	AR-DRG M01Z – Major male pelvic procedures (public)	$13,874		
Anaesthesia	INITIATION OF MANAGEMENT OF ANAESTHESIA for radical prostatectomy	$187.00	MBS item 20845	Based on a procedure time of between 171 and 180 minutes.
	2:51 HOURS TO 3:00 HOURS	$261.80	MBS item 23114	
Pathology	Examination of complexity level 7 biopsy material with multiple tissue blocks, including specimen dissection, all tissue processing, staining, light microscopy and professional opinion or opinions—1 or more separately identified specimens	$470.00	MBS item 72838	Excised tissue is sent for histopathological review.
Packed red blood cells		$32.90	(Medical Services Advisory Committee 2006)	$329 per unit, assume 2 units in 5% of patients.
Transfusion		$7.88		$78.80 per transfusion, assume 2 transfusions in 5% of patients.

Component	Description	Cost (full fee)	Source of estimate	Rationale and assumptions
Cross-matching for blood	Compatibility tests by cross-match—all tests performed on any one day for up to 6 units, including: (a) all grouping checks of the patient and donor; and (b) examination for antibodies and, if necessary, identification of any antibodies detected; and (c) (if performed) any tests described in item 65060, 65070, 65090 or 65096	$109.65	MBS item 65099	Done on all patients

Table 40 Unit costs of services and medications relating to active surveillance for localised prostate cancer over a 12-month period

Component	Description	Cost (full fee)	Source of estimate	Rationale and assumptions
Initial urologist consult	As brachytherapy Table 37 above	$80.85	MBS item 104	Regardless of final treatment decision, men will be seen initially by a urologist.
Initial radiation oncologist consult	As brachytherapy Table 37 above	$80.85	MBS item 104	Prior to patient deciding on active surveillance, they may wish to consult a radiation oncologist regarding radiotherapy options (LDRBT, EBRT)
Re-biopsy	PROSTATE, transrectal needle biopsy of, using transrectal prostatic ultrasound techniques and obtaining 1 or more prostatic specimens, being a service associated with a service to which item 55600 or 55603 applies	$265.40	MBS item 37219	Assume one biopsy done within a year to confirm appropriateness for active surveillance
	PROSTATE, bladder base and urethra, transrectal ultrasound scan of	$109.10	MBS item 55600	
	Examination of complexity level 4 biopsy material with 1 or more tissue blocks, including specimen dissection, all tissue processing, staining, light microscopy and professional opinion or opinions—12 to 17 separately identified specimens	$210.35	MBS item 72827	
	Total cost for prostate biopsy in the first 12 months	$584.85	37219 + 55600 + 72827	
PSA blood test	Prostate specific antigen – quantitation in the monitoring of previously diagnosed prostatic disease (including a test described in item 66655)	$81.20	MBS item 66656 x 4 (per year)	Patients will receive 4 PSA tests each year for the duration of active surveillance.
Follow-up consultation by urologist	Each attendance SUBSEQUENT to the first in a single course of treatment	$162.40	MBS item 105 x 4 (per year)	Patients will visit a urologist 4 times per year for the duration of active surveillance. This likely represents an overestimation, in particular among men who remain on active surveillance for several years.
Transrectal ultrasound	PROSTATE, bladder base and urethra, transrectal ultrasound scan of	$109.10	MBS item 55600	From year 2 onwards, patients will receive a yearly transrectal ultrasound. (In year 1 all patients are assumed to receive a repeat biopsy, therefore an additional TRUS is unlikely to be required).

See Table 21 for a description of the management costs associated with active surveillance.

Glossary and abbreviations

3D-CRT	three-dimensional conformal radiotherapy (a type of EBRT)
ADT	androgen deprivation therapy
AHTA	Adelaide Health Technology Assessment
AIHW	Australian Institute of Health and Welfare
ANZAUS	Australian and New Zealand Association of Urological Surgeons
AR-DRG	Australian Refined Diagnosis Related Groups
AS	active surveillance
ASTRO	American Society for Therapeutic Radiology and Oncology
AUA	American Urological Association
AUASI	American Urological Association Symptom Score
bNED	biochemical no evidence of disease (freedom from biochemical recurrence)
BR	biochemical recurrence
BT	brachytherapy
CT	computerised tomography
CTC	Clinical Trials Centre
D90	the dose delivered to 90% of the planned radiotherapy target
EAU	European Association of Urology
EBRT	external beam radiotherapy
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	EORTC quality of life questionnaire – cancer
EORTC QLQ-PR25	EORTC quality of life questionnaire – prostate cancer module

EPIC	Expanded Prostate cancer Index Composite
FACT-P	Functional Assessment of Cancer Therapy – prostate module
Gleason grade	a measure of the aggressiveness of prostate cancer from 1 (well-differentiated, least aggressive) to 5 (undifferentiated, most aggressive)
Gleason score	the sum of the two most common Gleason grades
HRQoL	health-related quality of life
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
IIEF	International Index of Erectile Function
IMRT	intensity modulated radiotherapy (a type of EBRT)
IPSS	International Prostate Symptom Score
LDR	low dose rate
LDRBT	low-dose-rate brachytherapy
LHRHa	luteinising hormone releasing hormone analogue
LUTS	lower urinary tract symptoms
MBS	Medicare Benefits Schedule
MRI	magnetic resonance imaging
MSAC	Medical Services Advisory Committee
NCCN	National Comprehensive Cancer Network
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Clinical Excellence
NSW	New South Wales
PBS	Pharmaceutical Benefits Scheme
PSA	prostate specific antigen

PYLL	potential years of life lost
QALY	quality adjusted life year
RALP	robot-assisted laparoscopic prostatectomy
RCT	randomised controlled trial
RP	radical prostatectomy
RTOG	Radiation Therapy Oncology Group
SA	South Australian
SF-36	Short Form–36 health survey (a questionnaire of 36 questions developed to measure HRQoL)
SPC	second primary cancer
TG-43	(or AAPM TG-43) American Association of Physicists in Medicine Task Group 43—a report outlining a dosimetry protocol to standardise the methods used to calculate dose to patients receiving brachytherapy
TNM	Tumour–nodes–metastases
TRUS	transrectal ultrasound
TURP	transurethral resection of the prostate
UCLA-PCI	University of California, Los Angeles – Prostate Cancer Index
UICC	Union Internationale Contre le Cancer
USANZ	Urological Society of Australia and New Zealand

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