Brachytherapy for the treatment of prostate cancer

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Assessment report

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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.

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

This report was prepared by the Medical Services Advisory Committee with the assistance of Mr Luke Marinovich, Dr Sarah Lord, Ms Alison Griffiths and Dr Simon Eckermann from the NHMRC Clinical Trials Centre, University of Sydney. The report was edited by Ms Merry Pearson. The recommendation was endorsed by the Minister for Health and Ageing on 28 November 2005.

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Brachytherapy is the implantation of radioactive sources in or near tumours. When used in the treatment of prostate cancer, radioisotopes are inserted directly into the prostate gland guided by a transrectal ultrasound probe as a single day-patient or overnight stay procedure. The radioactive sources have a localised effect and, when the placement and dosage are planned appropriately, destroy tumour cells of the prostate gland without significantly irradiating adjacent normal tissue. The total radiation dose is about twice that from conventional external beam radiotherapy (EBRT), and about 50 per cent higher in terms of biological equivalence.

There are two types of prostate brachytherapy—permanent implants (using small iodine 125 (I 125) or palladium 103 (Pd 103) seeds) and temporary implants (using iridium 192 wires via temporary catheters). Only permanent implants using I 125 are the subject of this application. Palladium implants are not currently available in Australia.

Brachytherapy has been proposed to offer a more efficient treatment (shorter treatment, in-hospital and recovery time) for localised prostate cancer with the additional advantages of limiting the side-effects to adjacent tissues that occur with EBRT and the surgical risks associated with radical prostatectomy (RP). However, the procedure may be associated with short- and long-term complications.

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. 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.

A rigorous assessment of evidence is thus the basis of decision making when funding is sought under Medicare. A team from the NHMRC Clinical Trials Centre was engaged to conduct a systematic review of literature on brachytherapy for early localised prostate cancer. An Advisory Panel with expertise in this area then evaluated the evidence and provided advice to MSAC. This review updates MSAC's initial assessment of prostate brachytherapy published in 2000.

Approach to assessment

Review question

This report summarises MSAC's assessment of the current evidence available to address the review question:

What is the safety, effectiveness and cost-effectiveness of I 125 brachytherapy for treating early localised prostate cancer (staged as T1 or T2 N0M0, with a Gleason score of ≤6, and a PSA of ≤10) compared with radical prostatectomy, external beam radiation therapy, and no initial treatment or deferred treatment (active surveillance)?

The outcomes assessed included survival; tumour progression; urinary, rectal and sexual function; quality of life and costs.

Literature review

The medical literature was searched to identify relevant primary studies and systematic reviews for the period between 1999 and February 2005. Searches were conducted via electronic databases including Medline, Pre-Medline, Embase, Current Contents, CINAHL, EBM and HTA websites, and by scanning reference lists. The search was limited by publication date in order to update MSAC's previous assessment of brachytherapy for prostate cancer, published in 2000.

The search strategy retrieved 1,663 non-duplicate citations. These were screened by one reviewer using prespecified eligibility criteria, with a representative sample of 668 citations (40%) screened by a second reviewer. All potentially eligible articles identified using were independently assessed for eligibility and quality by both reviewers.

Thirteen systematic reviews of case series and comparative studies (Level III-2) and four comparative, non-randomised cohort studies (Level III-2) were eligible for this review. No randomised controlled trials were identified.

MSAC's assessment of brachytherapy for the treatment of prostate cancer

Clinical need

Epidemiology

Excluding non-melanoma skin cancer, prostate cancer is the most common cancer diagnosed in Australian males (AIHW 2004a). It is the second leading cause of cancer deaths in males after lung cancer (AIHW 2004a). In 2001, 11,191 new cases of prostate cancer and 2,718 prostate cancer deaths were recorded by Australian State and Territory cancer registries, representing 23 per cent of all male cancers and 13 per cent of all male cancer deaths (AIHW, 2005b). The incidence of prostate cancer increases with age. The average age at first diagnosis in Australian males was 71 years in the year 2000 (AIHW 2004b).

The age standardised annual incidence rate has been relatively stable at around 128 cases per 100,000 men since 1996, following a sharp rise in the previous decade, a trend attributed to an increase in the diagnosis of early stage disease as a result of PSA screening (AIHW 2004b). In comparison to the high incidence of prostate cancer, the overall death rate in Australian men was 35 deaths per 100,000 in 2002, reflecting the relatively low case fatality rate associated with this disease.

In Australia, the five-year relative survival rate for prostate cancer was reported at 82 per cent between 1992 and 1997. This represents a 25 per cent increase since the period between 1982 and 1986 (AIHW 2004b). Data from cancer registries in the United States have shown that survival for local disease reaches 100 per cent compared to 33.5 per cent for distant disease (NCI, 2001).

Potential utilisation

Using staging data from hospital-based cancer registries it is estimated that up to 6,823 Australian males per year may potentially be eligible for the treatment of early prostate cancer.

In 2004, the number of brachytherapy-related services funded through the Medicare Benefits Schedule ranged from 295 (item 15338: radiation oncology services for implanation of prostate brachytherapy seeds) to 336 (item 15339: dosimetry planning services). These MBS figures have steadily increased since the introduction of interim funding for prostate brachytherapy in 2001.

Trends from the United States suggest that brachytherapy may increasingly replace prostatectomy in this low risk patient group (Cooperberg, Lubeck, Meng et al, 2002).

Safety

Conclusions about the comparative safety of brachytherapy, EBRT and RP are based on two cohort studies (Level III-2 evidence). Findings from these studies indicate that brachytherapy is comparable to or better than RP and EBRT in terms of sexual functioning after treatment, and showed a relative advantage over both RP in terms of rates of post-treatment urinary continence. However, brachytherapy may result in higher rates of irritative or obstructive urinary symptoms than EBRT. These conclusions are consistent with the findings of 12 existing level III-2 systematic reviews that did not directly address the patient group and procedures specified for this review.

One study observed that brachytherapy resulted in worse stool incontinence after treatment than RP. Another study reported that brachytherapy may be comparable to EBRT for grade 2 rectal toxicity. Systematic reviews reported disparate conclusions regarding the relative advantage, disadvantage or comparability of brachytherapy compared with other treatments for bowel/rectal functioning.

Effectiveness

Four cohort studies provided outcome data to directly address the relative effectiveness of brachytherapy compared to EBRT and RP (level III-2 evidence). No evidence was identified for a direct comparison of effectiveness in patients treated with brachytherapy compared to active surveillance.

The evidence available to date does not demonstrate a difference in survival or disease progression between brachytherapy, RP and EBRT in patients with early localised prostate cancer. No primary studies or systematic reviews were identified that compared survival rates between brachytherapy, RP, EBRT and active surveillance. One study observed a modest statistically significant advantage in relapse free survival for radical prostatectomy compared to brachytherapy (Borchers, Kirschner-Hermanns, Brehmer et al 2004); however, some patients included in this study did not appear to fufill the criteria for early localised prostate cancer used for this review. The advantage reported in this study was not observed in two other studies.

Ten level III-2 systematic reviews reporting on the effectiveness of brachytherapy in a broader patient population or using broader definitions for brachytherapy and comparators also concluded that a difference in disease progression between brachytherapy, RP and EBRT could not be demonstrated.

Issues in the interpretation of evidence

- It is possible that the studies reviewed are not large enough (insufficiently powered) or that the study timeframes are too short to detect true clinically significant differences between treatments.
- Given that the studies are non-randomised and the criteria for selection of patients to each treatment type are largely unknown it is also possible that study bias may obscure the true relative effects of these treatments.
- Variation between the characteristics of included studies in the provision of neoadjuvant or adjuvant androgen deprivation therapy, pretreatment prostate volume, the definitions of safety domains and treatment failure, and the length of follow-up precludes the synthesis of this evidence.
- The strength of the evidence provided by the systematic reviews is limited by the variation in characteristics of the primary studies and in the quality of the methods and reporting of the systematic reviews themselves.
- The relevance of the systematic reviews to the research question specified for this assessment also varied considerably in terms of the implant types assessed and the populations studied.
- Hence, the previously mentioned conclusions should be interpreted with caution. Conclusions regarding bowel/rectal function should be approached with particular caution, given the absence of converging conclusions from previous systematic reviews. Prospective trials are required to draw more definitive conclusions about the relative effect (or non-inferiority) of prostate brachytherapy.

Cost-effectiveness

Direct costs of brachytherpy treatment relative to radical prostatectomy RP and ERBT have been estimated for an Australian setting, with the expected costs of brachytherapy ($14,050) higher than RP ($10,137) or ERBT ($9,266). These costs do not, however,

include costs of follow-up treatment, or any potential societal benefit of fewer days off work. UK modelling of expected quality adjusted life years (QALYs) allowing for differences in adverse event rates in 65 year old patients with moderately differentiated tumors, suggests brachytherapy has higher expected QALYs (8.02) than RP (7.78), EBRT (7.47) or active surveillance (7.52). This gain in QALYs is, however, highly sensitive to modelled adverse event rates, with brachytherapy less effective than each of the other strategies in a worst case scenario. Further research into comparative treatment effects on adverse events as well as survival is required before conclusive recommendations can be made about the effects, costs or cost-effectiveness of strategies.

Recommendation

Following a reassessment of further evidence pertaining to the safety, effectiveness and cost-effectiveness of brachytherapy for the treatment of prostate cancer, interim public funding should continue for patients with prostate cancer meeting the following criteria:

- at clinical stages T1 and T2 with Gleason scores of less than or equal to 6, prostate specific antigen (PSA) of less than or equal to 10 ng/ml, gland volume less than 40 cc and with life expectancy of more than 10 years; and

- where the treatment is conducted at approved sites.

- The Minister for Health and Ageing accepted this recommendation on 28 November 2005.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of brachytherapy, which is a therapeutic technology for the treatment of early localised prostate cancer. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer affairs and health administration.

This report summarises the assessment of current evidence for brachytherapy for early localised prostate cancer. It updates MSAC's initial assessment of this procedure that was published in 2000.

Background

Previous MSAC assessment

MSAC initially conducted a review of the safety, effectiveness and cost-effectiveness of brachytherapy for prostate cancer in 2000 (MSAC). This review compared brachytherapy with the alternative treatments of radical prostatectomy (RP), external beam radiation therapy (EBRT), and no initial treatment or deferred treatment (previously known as 'watchful waiting', now superseded by the term 'active surveillance'). No randomised controlled trials (RCTs) were identified and conclusions about effectiveness were limited to Level III–IV evidence. The report noted that the profile of adverse events differed between brachytherapy and the alternative treatments, with brachytherapy possibly resulting in a higher rate of potency preservation than the comparators, although the overall incidence in adverse events appeared to be similar. A basic costing analysis was used to estimate an additional direct cost of $3500 per patient for brachytherapy compared with radical prostatectomy.

These findings led to MSAC's recommendation for interim public funding of brachytherapy conducted at approved sites for patients with early localised prostate cancer. The current report updates this initial assessment to report on relevant evidence published since 1999.

Brachytherapy

The procedure

Brachytherapy is the implantation of radioactive sources in or near tumours. When used in the treatment of prostate cancer, radioisotopes are inserted directly into the prostate gland guided by a transrectal ultrasound probe. Implantation is carried out as single day-patient or overnight stay procedure. The radioactive sources have a localised effect and, when the placement and dosage are planned appropriately, destroy tumour cells of the prostate gland without significantly irradiating adjacent normal tissue.

There are two types of prostate brachytherapy—permanent implants using small iodine 125 (I 125) or palladium 103 (Pd 103) seeds) and temporary implants (using iridium-192 wires via temporary catheters). Permanent I 125 implants only are the subject of this application. Palladium implants are not currently available in Australia.

Since 1984, radioactive seeds have generally been implanted via the perineal percutaneous route. Before 1984, brachytherapy was conducted with an open operation, often with pelvic lymph node dissection, and seeds were placed randomly. This approach proved ineffective and is no longer used. Data using this approach have not been considered as part of this review.

Each I 125 implant seed usually has an activity of 11 to 15 MBq (0.3–0.4 mCi), with the dosage occurring within the range of 7 to 26 MBq (0.18–0.70 mCi). Between 70 and 100 seeds are typically inserted. The total radiation dose is about twice that from conventional external beam radiotherapy, and about 50 per cent higher in terms of

biological equivalence, but implantation allows the radiation field to be concentrated more directly in the target area. Implantation may be used with neoadjuvant hormonal therapy to decrease the tumour volume. It is also sometimes combined with EBRT as 'combination therapy'. The procedure requires the combined services of a urological surgeon and a radiation oncologist. A medical physicist/radiation therapist also participates in the procedure through their roles in planning treatment and supervising radiation safety. Patients are usually referred to a urologist specialising in this technique or a radiation oncologist.

Brachytherapy has been proposed to offer an efficient treatment (short treatment, in-hospital and recovery time) for localised prostate cancer which has the advantage of limiting the side-effects to adjacent tissues that occur with EBRT and the surgical risks associated with prostatectomy. However, the procedure may be associated with short- and long-term complications.

Intended purpose

Brachytherapy is intended for the treatment of early localised prostate cancer. In Australia, brachytherapy is intended to be used in patients with:

- T1 or T2 N0M0 disease using the TNM staging system;
- Gleason scores less than or equal to 6; and
- prostate specific antigen (PSA) levels less than or equal to 10 ng/ml.

The definitions of these clinical staging and grading systems are described in the following section.

Classification of prostate cancer

Staging and grading of cancer is performed to predict prognosis and guide therapy. Strategies for determining the stage and grade of a cancer include:

- histopathological grading of biopsy or surgical specimens;
- diagnostic imaging (ultrasound, computed tomography [CT] scans and radionuclide bone scans); and
- surgical staging by biopsy and histological examination of pelvic lymph nodes.

The three methods for classifying prostate cancer referred to in this review are described briefly as follows.

Tumour–nodes–metastases staging

Using the tumour–nodes–metastases (TNM) staging system, prostate cancer is staged according to the size of the primary tumour (T), the extent of the involvement of regional lymph nodes (N) and the presence of metastases (M) (see Table 1). TNM staging was initially adopted by the American Joint Committee of Cancer and the International Union Against Cancer in 1992. Changes were made in 1998 reducing the subdivision of the T2 category into T2a and T2b; however, the original T2 classification was reinstated

in 2002 (Table 1). These changes make it difficult to compare outcomes of treatment by stage from different time periods; however, most studies included in this review report on patients diagnosed before 1997 (either stated or assumed due to length of follow-up time) and are likely to have been staged using the original TNM classification.

Table 1 Tumour–nodes–metastases (TNM) clinical classification of stage of prostate cancer[a]

Classification	Definition
T classification	Primary tumour
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour not palpable or visible by imaging
T1a	Tumour incidental histologic finding in 5% or less of tissue resected
T1b	Tumour incidental histologic finding in more than 5% of tissue resected
T1c	Tumour identified by needle biopsy (eg because of elevated PSA)
T2[b]	Tumour confined within prostate
T2a	Tumour involves one 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 prostatic capsule
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, or pelvic wall.
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 metastasis
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

a American Joint Committee on Cancer (AJCC) *Cancer Staging Manual* (Greene, Page, Flemming et al 2002).
b Alternate AJCC 1998 classification: T2a = tumour involves one lobe; T2b = tumour involves both lobes (AJCC 2002).

Gleason score

The Gleason score uses a histopathological classification system to grade the differentiation of the tumour cells from 1 (well differentiated, least aggressive) to 5 (undifferentiated, most aggressive). It is calculated from the combined grade of two different sections of the tumour (the most prevalent grade summed with the second most prevalent grade). In combination with clinical staging it is used as a predictor of prognosis. Table 2 describes the classification of Gleason scores. There is considered to be significant prognostic differences within the Gleason score of 7, depending on the most prevalent grade (4 +3 versus 3 + 4) (Che & Grignon 2002).

Table 2 Classification of grade of prostate tumour (Gleason score)

Gleason score	Histopathology
G 2–5	Well differentiated
G 6–7	Moderately differentiated
G 8–10	Poorly differentiated or undifferentiated

Prostatic specific antigen

PSA is a glycoprotein enzyme that is produced in the prostate. A blood sample is used to measure the serum concentration of PSA (referred to as the PSA level). The normal serum concentration of PSA increases with age up to 6.5 ng/ml in men over the age of 70 years (Oesterling, Jacobsen, Chute et al 1993). Raised PSA levels in the blood are associated with prostate cancer, benign prostatic hypertrophy and prostatitis.

In the past, pretreatment PSA levels have been shown to be an important predictor of disease stage and prognosis in patients with prostate cancer (NHMRC 2003). Zietman, Coen, Shipley et al (1994) reported that patients with localised disease using the TNM classification (T1–T2 cancer) and baseline PSA levels higher than 15 ng/mL may have outcomes as poor as those with T3–T4 disease and even worse than T3–T4 patients with lower baseline PSA levels. However, a recent epidemiological study reported that PSA may be less useful as a prognostic marker in populations where broad PSA screening has led to the early detection of disease (Stamey, Caldwell, McNeal et al 2004). In this retrospective study of 1,317 radical prostatectomy cases, Stamey, Caldwell, McNeal et al (2004) observed that PSA levels were statistically significantly related to cancer volume, Gleason score, capsular penetration, lymph node involvement, seminal vesical invasion and prostate weight in patients undergoing RP between 1983 and 1988; however, in the period from 1999 to 2003, PSA levels were only associated with prostate weight.

Despite these questions about the ongoing value of PSA levels as a prognostic marker in newly detected disease, PSA levels continue to be useful as a marker of tumour activity, indicating persistent local disease or the development of subclinical metastases after treatment, as described in the following.

Monitoring

The Australian clinical practice guidelines for the management of localised prostate cancer note that studies are increasingly using measures such as PSA to monitor tumour progression (NHMRC 2003). This is largely due to the traditional clinical definitions of treatment failure (development of palpable local recurrence, or radiologically or symptomatically evident distant metastasis) requiring observation for a long period of time. The American Brachytherapy Society has published guidelines for the use of PSA for monitoring disease progression after radiation therapy, stating that three consecutive rises in post-treatment PSA is a reasonable definition of biochemical failure (Cox, Grignon, Kaplan et al 1997). For research purposes, PSA should be measured every three to four months for the first two years, and then six-monthly thereafter. However, no definition of PSA failure has been shown to be a surrogate for clinical progression or survival. Cox, Grignon, Kaplan et al (1997) also state that although PSA nadir after treatment has strong prognostic value, no specific cut-off point can be determined to delineate successful from unsuccessful treatment.

Despite the publication of guidelines designed to improve consistency in monitoring and the way it is reported, great variations exist in the definitions of biochemical failure (or biochemical disease-free survival [bDFS]) used in the literature, both within and between treatments. Some studies employ the sequential rise in PSA recommended by the American Brachytherapy Society; some define treatment failure in terms of PSA nadir; others define failure by the need for adjuvant drug therapies; and still others employ various combinations of these criteria. Often, studies comparing different treatments use different definitions of biochemical failure for each treatment.

Contraindications

Brachytherapy is relatively contraindicated in patients:

- with a recent history of a transurethral resection of the prostate (TURP), depending on the size of the cavity and extent of the surgery;
- who have severe urinary obstructive symptoms because they would be at risk of severe obstruction after implantation therapy; and
- with a prostate size of greater than 40 ml depending on the pelvic bony anatomy because of difficulties with seed implantation; however, patients with a prostate gland greater than 40 ml but less than 50 ml may be treated with 3 to 6 months of androgen blockade to decrease the prostate size, making the prostate gland more suitable for brachytherapy.

It is generally accepted that brachytherapy should only be considered for patients who have a life expectancy of more than ten years, as any improved survival time is only likely to occur in this group. Patients who have a Gleason score of 7 or more or a PSA of greater than 10 have a higher probability of relapse and are not normally treated by brachytherapy alone. Such patients have been treated by combined brachytherapy and EBRT. The use of brachytherapy in this setting is not addressed in this review.

Assessment of adverse events

One of the problems encountered when attempting to compare the safety of the different treatment options for early prostate cancer is the lack of standardised tools for the measurement of these outcomes. The American Brachytherapy Society recommends that all studies investigating brachytherapy report data on urinary, sexual, and bowel function using the International Prostate Symptom Score, International Index of Erectile Function, and Radiation Therapy Oncology Group toxicity grading criteria, respectively. They also provide additional parameters for reporting on urinary, rectal, and sexual symptoms that are specifically relevant to brachytherapy (Nag, Ellis, Merrick et al 2002).

Australian data on side-effects is not yet available. The Australasian Brachytherapy Group has developed a standardised database to record patient demographics, implant parameters, urinary, rectal and sexual morbidity, and outcomes, and has recommended that all groups in Australia should collect the data prospectively.

The Therapeutic Goods Administration (TGA) collects Australian safety data for brachytherapy regarding mechanical failures of the equipment used, but does not collect data on adverse events related to therapy.

Clinical need / burden of disease

Natural history of disease

Epidemiological studies have indicated that prostate cancer is a heterogeneous disease (NHMRC 2003). Histologic evidence of prostate cancer can be found in 30 to 40 per cent of men aged above 50 years, but only 1 in 4 of these cancers will become clinically evident and only 1 in 14 will be the cause of death (Abbas & Scardino 1997).

A recent population-based cohort study of 223 men with early stage (T0–T2, NX, M0) initially untreated prostate cancer and a mean observation period of 21 years has recently provided long-term data on the natural history of early localised disease (Johansson, Andren, Andersson et al 2004). The authors reported that although most early localised prostate cancers did not result in death in the first 15 years (prostate cancer mortality rate 15/1000 person years), the death rate increased to 44/1000 person years beyond that time, with a decrease in cumulative progression free survival from 45 to 36 per cent, survival without metastases from 76.9 to 51.2 per cent and prostate-specific survival from 78.7 to 54.4 per cent.

One of the primary challenges in managing patients with prostate cancer at an early clinical stage is that it is not possible to differentiate clinically significant tumours from those that may not progress to generalised disease. While histological, biochemical and molecular markers exist, these currently have limited ability to predict prognosis, although they have been useful as markers for progression in early stage disease.

Epidemiology

Incidence and mortality rates

Excluding non-melanoma skin cancer, prostate cancer is the most common cancer diagnosed in Australian males and the third most common cancer diagnosed in Australians overall (men and women) after colorectal cancer and breast cancer (AIHW 2004a). It is the second leading cause of cancer deaths in males after lung cancer (AIHW 2004a).

In 2001, 11,191 new cases of prostate cancer and 2,718 prostate cancer deaths were recorded by State and Territory cancer registries in Australian male residents (AIHW 2005b). These figures represent 23 per cent of all male cancers and 13 per cent of all male cancer deaths for that year. The incidence rate of prostate cancer has been relatively stable since 1996, with an age standardised annual incidence rate at around 128 cases per 100,000 men, following a sharp rise in the previous decade, which peaked in 1994 with 13,045 recorded cases (AIHW 2005b). This trend has been attributed to an increase in the diagnosis of early stage disease as a result of PSA screening (AIHW 2004b). Similar trends have been observed in the United States (SEER Cancer Statistics Review, 1975–2001).

The incidence of prostate cancer increases with age. The average age at first diagnosis in Australian males was 71 years in the year 2000 (AIHW 2004b). The disease is very rare in patients younger than 55 years of age; incidence rates rise steeply after age 60 (350.8/100,000) reaching 1,065.7/100,000 in men 85 years and older. In comparison to

the high incidence of prostate cancer, the overall death rate in Australian men was 35/100,000 in 2002, reflecting the relatively low case fatality rate associated with this disease. Mortality rates have recently been decreasing in Australia, with a 1.1 per cent annual reduction reported between 1998 and 2002 from a high rate of 44/100,000 in the early 1990s (AIHW 2004b).

The overall burden of a disease can be described as years of life lost (YLL) due to early disease, person life years lost (PLYL) per year or years of healthy life lost due to disability (YLD). Disability adjusted life years (DALY) combine YLL and YLD to provide a broad population measure of burden of disease, which is defined as incident lost years of healthy life. The PLYL due to prostate cancer in persons diagnosed before age 75 years was estimated at 5,665 life years in 2001, compared to lung cancer at 44,978 PLYL, colorectal cancer at 29,768 PLYL and breast cancer at 28,733 PLYL (AIHW 2004a). These differences have been attributed to the relatively late age of onset of prostate cancer and the moderate aggressiveness of the disease (AIHW 2004a). Similarly, lung cancer accounted for 24 per cent of the DALYs in males in 1996, compared to colorectal cancer at 14 per cent and prostate cancer at 13 per cent (AIHW 2004b).

Survival rates

In Australia, the five-year relative survival rate for prostate cancer was reported at 82 per cent between 1992 and 1997. This represents a 25 per cent increase since the period between 1982 and 1986 (AIHW 2004b). Data from cancer registries in the United States have shown that survival for local disease reaches 100 per cent compared to 33.5 per cent for distant disease (SEER Cancer Statistics Review 1975–2001).

Potential utilisation

There is currently no ongoing population-based collection of prostate cancer staging information in any Australian State or Territory (Threlfall & Thompson 2004). However, hospital-based staging data are collected in some States. Data from South Australian hospital-based cancer registries indicate that 19 per cent of all incident prostate cancers were classified as T1N0M0 and 42 per cent as T2N0M0 (Delaney 2003). Applying these data to the overall incidence rate of prostate cancer in Australia in 2001, we can estimate that up to 6,823 Australian males per year may potentially be eligible for the treatment of early prostate cancer.

Utilisation is recorded by the Health Insurance Commission (HIC) based on the number of services claimed for brachytherapy-specific items on the Medicare Benefits Schedule (MBS) as shown in Table 3. Item 55603 involves transrectal ultrasound (TRUS) scanning, and is related to brachytherapy planning but is not specific to prostate brachytherapy. Hence utilisation data are significantly higher for this item. The remaining items are dedicated to prostate brachytherapy, and are divided into planning with localisation (15513) and dosimetry (15539) components, and radioactive seed implantation with urological (37220) and radiation oncology (15338) components (HIC 2005). Table 3 shows the increase in utilisation over the period 2001 to 2004, following MSAC's recommendation for interim funding in 2000.

Table 3 Medical Benefits Scheme item numbers and utilisation for prostate brachytherapy

		Number of services			
Item	Description	2001	2002	2003	2004
55603	PROSTATE, bladder base and urethra, transrectal ultrasound scan of.	5,970	6,872	9,172	13,079
15513	RADIATION SOURCE LOCALISATION using a simulator or x-ray machine or CT for brachytherapy treatment planning for I 125 seed implantation of localised prostate cancer.	3	110	217	289
37220	PROSTATE, radioactive seed implantation of, using transrectal ultrasound guidance, for localised prostatic malignancy. The procedure must be performed by a urologist in association with a radiation oncologist.	2	107	177	307
15338	PROSTATE, radioactive seed implantation of, using transrectal ultrasound guidance, for localised prostatic malignancy. The procedure must be performed by a radiation oncologist in association with a urologist.	3	107	160	295
15539	BRACHYTHERAPY PLANNING, computerised radiation dosimetry for I 125 seed implantation of localised prostate cancer.	3	100	177	326

HIC data measure the number of services billed to private patients and public patients treated in private hospitals, but they do not capture treatments to public patients in public hospitals, which explains the discrepancy between HIC data and manufacturers supply figures. The National Hospital Morbidity Database provides information about the number of interstitial brachytherapy procedures involving permanent implants in public and private hospitals (ICD-10-AM 1792: 15327-04, 15327-05). During the 2002–03 financial year, 171 interstitial brachytherapy procedures involving permanent implants were recorded (compared to 137 urological brachytherapy services billed to the HIC over the same period, suggesting 20 per cent of services were performed on public patients in public hospitals). These data more closely approximate the manufacturers supply data; however, these ICD-10AM codes do not distinguish between different disease sites or stages and so this figure may overestimate the use of permanent implants for treating localised prostate cancer (AIHW, 2005a).

In comparison to these estimates of brachytherapy utilisation, 3,413 open prostatectomy procedures were recorded between 2002 and 2003 (stage of disease not available) (ICD-10-AM code 1167, AIHW 2005a). ICD-10AM codes for radiotherapy services are not available by site or stage of disease for comparison with these data.

Trends have been observed in treatment modality rates in the United States of America. Cooperberg, Lubeck, Meng et al (2002) reported an increase in the use of brachytherapy in low-risk patients from 3.1 to 12.0 per cent between 1999 and 2001, and a corresponding decline in the prostatectomy rate over the same time period from 63.8 to 51.6 per cent. Hence brachytherapy may increasingly replace prostatectomy in this patient group.

Existing procedures

The optimal management of localised prostate cancer remains controversial. Few studies adequately compare the current treatment options. Rapid developments in the area also mean that long-term data on the treatment methods in current use are not available.

The most commonly used options for managing localised prostate cancer are summarised as follows. For a more complete discussion of these therapies, see the NHMRC report *Clinical Practice Guidelines: Evidence-based information and recommendations for the management of localised prostate cancer* (2003).

Comparators

Radical prostatectomy

RP is the complete surgical removal of the prostate gland and seminal vesicles. It may be performed as an open procedure using a retropubic or perineal approach or laparoscopically. The retropubic approach is performed with a lower midline incision of around 9 cm between the umbilicus to the top of the pubis (Carroll, Meng, Downs et al 2002). Pelvic lymphadenectomy can be performed through this incision prior to removing the prostate or laparoscopically. The perineal approach is performed with a curvilinear incision between the ischial tuberosities (the lateral points on the bony pelvis) with a separate incision or laparascopic approach for pelvic lymphadenectomy (Melman, Boczko, Figueroa et al 2004). The retropubic approach allows easier identification and sparing of the neurovascular bundles responsible for erectile function (Walsh 2000), while the perineal approach results in reduced blood loss (Sullivan, Weir, Kinahan et al 2000).

When performed laparoscopically, access ports are placed through small incisions made near the umbilicus and in the lower abdomen. The surgeon performs the operation using handheld instruments passed through these ports while an assistant holds a fibre-optic viewing camera (Schuessler 1997). More recently, a robotic-assisted laparoscopic technique has been introduced where the surgeon operates using minature robotic telescope and robot arms operated from a remote console (Smith 2004). The potential advantage of these minimally invasive techniques are reduced length of hospital stay and convalescence with comparable local tumour control (Guillonneau, El-Fettouh, Baumert et al 2003).

RP is a major operation with an average operating time of 2 to 5 hours using open or laparoscopic techniques (Anastasiaids, Salomon, Katz et al 2003; Sullivan, Weir, Kinahan et al 2000; Poulakis, Dillenburg, Moeckel et al 2005). It is rarely performed on men aged 70 or older due to the potential complications of the procedure and surgical contraindications due to existing co-morbidities, although it may be considered in those patients with greater than ten years' life expectancy. Australian Hospital Statistics data for Public and Private Hospitals (AIHW 2005a) show that the mean hospital stay following open prostatectomy was 8.5 days in 2002–2003 (ICD-10AM code 1167). There is no unique ICD-10AM code for laparoscopic prostatectomies for comparison. The figure for open RPs includes patients undergoing prostatectomy for any cause or stage of disease and is likely to overestimate the median length of stay due to the inclusion of patients with severe complications and lengthy admissions. The Advisory Panel has estimated the current median hospital stay following open RP at around 4.5 days in Australia (Advisory Panel March 2005). However, shorter average stays of 2 to 3 days have recently reported in the literature for open (Lepor 2003) and laparoscopic (Wilson, Kennett & Gilling 2004) procedures.

The complication rates for RP are variable and have decreased with improved surgical techniques (Walsh 2000). Surgical mortality rates of up to 1 per cent have been reported

in case series (NHMRC 2003). Urinary incontinence and impotence are two of the most commonly reported complications. Rectal complications have also been reported. Due to non-standardised definitions and differing survey techniques, reports on severity and frequency of disability vary considerably and may underestimate true patient function (NHMRC 2003; Krupski, Saigal, & Litwin 2003).

Rates of adverse events have improved with newer operative techniques (Walsh 2000). Specialised centres in the United States have reported recovery of urinary continence (requiring no use of continence pads) at up to 93 per cent, with younger men more likely to regain normal function (Walsh 2000; Kundu, Roehl, Eggener et al 2004). Walsh (2000) also reported that 86 per cent of patients regained sexual potency 18 months after RP using nerve-sparing techniques (n=62), while Kundu, Roehl, Eggener et al's (2004) series of 1,770 consecutive patients treated with bilateral nerve-sparing surgery reported normal erectile function in 76 per cent of preoperatively potent men younger than age 70 and 52 per cent in men over age 70.

External beam radiation therapy

EBRT is the irradiation of the prostate gland with radiation beams from an external source. Its primary advantage is its relatively non-invasive nature. It is an alternative for men who do not wish to have surgery or those with co-morbidities that increase the risks of surgery. It is given as an outpatient procedure on a regular basis for seven to eight weeks. Over the last decade, three-dimensional conformal radiation therapy (3DCRT) has been introduced to increase the radiation dose of EBRT by targeting the diseased tissue more accurately. It is performed with specialised imaging studies and computer software.

EBRT may result in urinary and rectal complications and sexual dysfunction (Nilsson, Norlen & Widmark 2004). Short-term urinary complications due to radiation effects on the bladder include urinary urgency, pain and frequency. These symptoms are usually mild, require conservative management only and resolve within weeks. Longer term urinary complications are rarer and include urethral stricture, cystitis and haematuria. A population-based study of EBRT complications in patients treated for clinically localised prostate cancer reported a statistically significant 3 per cent reduction in urinary control in 427 men at 24 months after diagnosis (Hamilton, Stanford, Gilliland et al 2001). Acute rectal complications include diarrhoea, rectal urgency, tenesmus and bleeding. These symptoms usually improve over time (Hamilton, Stanford, Gilliland et al 2001; Talcott, Manola, Clark et al 2003). Up to 3 per per cent of patients treated using modern techniques suffer severe rectal damage requiring intervention (Boersma, van den Brink, Bruce et al 1998). Erectile dysfunction is a common problem after EBRT, with rates of 40 to 50 per cent reported in the literature (Nilsson, Norlen & Widmark 2004). Again, studies investigating different EBRT and 3DCRT techniques in different populations have reported considerable variation in the frequency, type and duration of complications (Nilsson, Norlen & Widmark 2004).

It is difficult to compare studies of EBRT with those of prostatectomy patients, as the groups are often not comparable. A staging pelvic lymphadenectomy is often done in the latter group, but is rarely done in the radiotherapy group. Radiotherapy is usually used in those with more advanced disease, often in an older age group, and may include patients who were not fit for surgery. This means that data on the effectiveness of treatment are either not stratified by stage or are not comparable to data for patients who have undergone surgery.

No initial treatment or deferred treatment (active surveillance)

As already discussed, a proportion of patients who are diagnosed with prostate cancer do not progress to life-threatening disease. An approach sometimes termed 'active surveillance' (formerly 'watchful waiting'), may be used. This strategy delays treatment until the patient becomes symptomatic, develops complications from their prostate cancer, or has rising PSA. In some cases, routine biopsies may be performed every three to four months. Since there is currently no accurate way to distinguish tumours likely to progress to metastatic disease from those that pose little threat to life, there is a risk that a window of opportunity for a curative intervention may be missed if active surveillance is chosen. However, by deferring treatment, the patient avoids any potential complications from the more active forms of treatment. Deferred treatment may therefore be an option for elderly patients who may have short life expectancies.

Some data suggest that survival rates of men who are treated conservatively are not significantly lower than those treated with surgery or radiotherapy. However, the results of these studies should be interpreted with a high degree of caution—most are observational studies, for example, using data from population-based cancer registries, where the patients selected for active surveillance differ from those selected for treatment on important prognostic factors including grade of disease (for example, Chodak, 1994; Adolfsson, Steineck & Hedlund 1997; Borre, Nerstrom & Overgaard 1997; Brasso, Friis, Kjaer et al 1998). These potential selection biases impair the validity of the results.

Two RCTs have investigated differences in survival between patients randomised to RP versus active surveillance for the treatment of early prostate cancer (Iversen, Madsen and Corle 1995, Holmberg, Bill-Axelson, Helgesen et al 2002). In the first, Iversen, Madsen and Corle (1995) reported no difference in survival at 23 years for 142 men randomised to surgery or deferred treatment; however, flaws in this study (insufficient power to detect a clinically important difference, baseline differences between the treatment groups, no intention to treat analysis) make interpretation of these results difficult. More recently, Holmberg, Bill-Axelson, Helgesen et al (2002) reported a larger high quality trial (n=695) that demonstrated a prostate cancer-specific survival benefit for RP compared to active surveillance at a median of 6.2 years follow-up (hazard ratio [HR] 0.50, 95% CI 0.27–0.91). This study also reported that prostatectomy was associated with a reduced rate of distant metastases (HR 0.63, 95%CI 0.41–0.96), but did not show a statistically significant difference in overall mortality (HR 0.83, 95% CI 0.57–1.20). The impact of each option on different morbidity outcomes varied, with no overall differences in subjective quality of life (QoL) at four years (Steineck, Helgesen, Adolfsson et al 2002) At least 44 per cent of patients included in this trial did not meet the definition of early localised disease used in this review (74% stage T2 disease, subclassification not reported, 30% Gleason score >6, 44% pretreatment PSA > 10 ng/ml). Thus these findings may not be applicable to patients eligible for brachytherapy. Another RCT of poorer quality (unbalanced randomisation and 24% loss to follow-up) comparing hormonal treatment with active surveillance in 285 men also demonstrated a statistically significant difference in prostate cancer-specific survival with no difference in all cause mortality (Lundgren, Nordle & Josefsson 1995).

A comparison between brachytherapy and active surveillance is discussed further in the section 'Is it effective?'.

Other therapies

Other treatments are also being investigated for managing localised prostate cancer. One currently being evaluated is a combination of temporary brachytherapy with EBRT and conformal radiotherapy. The safety and effectiveness of this procedure are not yet adequately established.

High dose-rate (HDR) brachytherapy is typically used in high risk patients with more advanced disease. Research investigating HDR brachytherapy as a radiation boost to EBRT in these patients is ongoing; however, the safety and effectiveness of HDR brachytherapy as monotherapy in low risk patients is still unproven (Vicini, Vargas, Gustafson et al 2003).

These therapies are not addressed as comparators in the current review.

Marketing status of the device / technology

Brachytherapy is listed with the TGA as permanent transperineal prostate implants for curative brachytherapy of early stage prostate cancer: (AUST L67687 and AUST L58303).

Current reimbursement arrangement

Brachytherapy for prostate cancer currently receives interim funding under the MBS. There are five item numbers for planning, localisation of the radioactive source and implantation of radioactive seeds by a urological surgeon in association with a radiation oncologist at an approved site (Items 55603, 15513, 37220,15338 and 15539, as described in Table 3) (Australian Government Department of Health and Ageing 2004). Under this schedule, brachytherapy treatment is only recommended for patients with a gland volume of less than or equal to 40 ml and who have a life expectancy of at least 10 years. These item numbers specify that funding is only available for brachytherapy performed under ultrasound guidance for localised prostatic malignancy at clinical stages T1, T2A or T2B, with a Gleason score of less than or equal to 6 and a PSA of less than or equal to 10 ng/ml at the time of diagnosis (Australian Government Department of Health and Ageing 2004).

Current services

Brachytherapy may be performed at sites approved for the provision of radiation oncology services. The applicant has specified that there are currently 13 sites around Australia providing the service. It is currently performed by urologists and radiation oncologists as a subspecialty service. It is the expert opinion of the Advisory Panel that urologists and radiation oncologists should receive specialised training and should perform a minimum number of procedures per year to maintain skills.

Medical physicists working within radiation oncology units are required for treatment planning and radiation safety. There is currently a shortage of medical physicists in Australia relative to urologists and radiation oncologists. This has the potential to affect the feasibility of extending current brachytherapy services across Australia due to access

issues and the associated costs involved in employing and training additional medical physicists.

Approach to assessment

The research question

The review team worked with members of the Advisory Panel to develop specific questions addressing the use of brachytherapy for the treatment of early localised prostate cancer. These questions were formulated *a priori* based on information about the disease area, current practice and the intended purpose of the device.

A flow chart (see Appendix D) depicting the clinical pathways for treating prostate cancer was developed with the Advisory Panel. This flow chart was used to define the potential role of brachytherapy in the treatment of early localised prostate cancer. The population, intervention, comparator and outcomes defined for the primary review question are:

- population: patients with early localised prostate cancer staged as T1 or T2, with a Gleason score of less than or equal to 6, and a PSA of less than or equal to 10 ng/ml;
- intervention: brachytherapy (permanent I 125 implants);
- comparators: radical prostatectomy (RP), external beam radiation therapy (EBRT), active surveillance; and
- outcomes: survival, progression, quality of life, safety, costs.

Based on the clinical pathway flow chart, the following clinical question was developed and is addressed in this report:

- What is the safety, effectiveness and cost-effectiveness of I 125 brachytherapy for treating early localised prostate cancer compared with radical prostatectomy, external beam radiation therapy, and no initial treatment or deferred treatment (active surveillance)?

Definition of outcomes

In this review, bDFS as measured by post-treatment PSA levels is used as a measure of disease progression. Safety is considered in terms of sexual, urinary, and bowel/rectal functioning, which are the key domains defined by the American Brachytherapy Society in reporting morbidity after prostate brachytherapy (Nag, Ellis, Merrick et al 2002).

Review of literature

The MSAC's recommendations are based primarily on the findings of a systematic literature review conducted by the National Health and Medical Research Council Clinical Trials Centre (NHMRC CTC). The medical literature was searched to identify relevant primary studies and systematic reviews for the period between 1999 and February 2005. Searches were conducted via electronic databases as listed in Table 4. The

search was limited by publication date in order to update MSAC's previous assessment of brachytherapy for prostate cancer, published in 2000. Furthermore, compared with the previous review, the scope of the assessment was narrowed to include only comparative studies of brachytherapy and alternative treatments.

Table 4 Electronic databases searched in this review

Database	Period covered
Medline	1999–February 2005
EMBASE	1999–February 2005
Pre-Medline	1999–February 2005
Current Contents	1999–February 2005
CINAHL	1999–February 2005
All-EBM databases	–February 2005
—ACP Journal Club (ACP)	
—Cochrane Database of Systematic Reviews (COCH)	
—Database of Abstracts of Reviews of Effectiveness (DARE)	
—Cochrane Controlled Trials Register (CCTR)	

Search strategy

The search strategy was developed using the key elements of the clinical question. It contained search terms for both brachytherapy implants and interstitial irradiation and combined these with all the search terms for prostate cancer. The appropriateness of the terms and logic of the search strategy was reviewed by a specialist in electronic database searching.

The search strategy shown in Table 5 was used to identify papers in Medline. A similar search strategy using the same search terms was also employed for the EMBASE, Pre-Medline, Current Contents, CINAHL and all the EBM databases.

Table 5 Search strategy

Number	Search Terms
1.	prostate$ cancer.mp or Prostatic Neoplasms/
2.	exp NEOPLASMS/
3.	exp CARCINOMA/
4.	exp ADENOCARCINOMA/
5.	or/2-4
6.	exp Prostatic Diseases/
7.	exp PROSTATE/
8.	or/6–7
9.	5 and 8
10.	((carcinoma or neoplasm$ or adenocarcinoma or cancer$ or tumo?r$ or malignan$) adj3 prostat$).mp
11.	1 or 9 or 10
12.	brachytherap$.mp
13.	exp BRACHYTHERAPY/
14.	(interstitial irradiation or interstitial radiation).mp
15.	transperineal interstitial permanent prostate brachytherap$.mp
16.	prostat$ implant$.mp
17.	seed$.mp
18.	iodine implant$.mp
19.	((I or iodine) adj3 “125”).mp
20.	palladium implant$.mp
21.	((Pd or palladium) adj3 “103”).mp
22.	or/12–21
23.	11 and 22
24.	Animals/
25.	Human/
26.	24 not (24 and 25)
27.	limit 23 to yr=1999-2005
28.	27 not 26

Reference lists of publications were also searched for additional relevant citations that may have been inadvertently missed in searches of major databases.

In addition to the databases already listed, the websites of international health technology assessment (HTA) agencies listed in Table 6 were searched.

Table 6 Health Technology Assessment sites searched

Organisation	Website
International Network of Agencies for Health Technology Assessment (INAHTA)	www.inahta.org
British Columbia Office of Health Technology Assessment (Canada)	www.chspr.ubc.edu.ca/bcohta
Swedish Council on Technology Assessment in Healthcare (Sweden)	www.sbu.se
Oregon Health Resources Commission (USA)	www.ohppr.state.or.us/ohrc
Minnesota Department of Health (USA)	www.health.state.mn.us
Canadian Coordinating Office for Health Technology Assessment (Canada)	www.ccohta.ca
Alberta Heritage Foundation for Medical Research (Canada)	www.ahfmr.ca
Veteran's Affairs Research and Development Technology Assessment Program (USA)	www.va.gov/resdev
National Library of Medicine Health Service/Technology Assessment text (USA)	http://text.nlm.nih.gov
NHS Health Technology Assessment (UK)	www.hta.nhsweb.nhs.uk
Office of Health Technology Assessment Archive (USA)	www.wws.princeton.edu/~ota
Institute for Clinical Evaluative Science (Canada)	www.ices.on.ca
Conseil d'Evaluation des Technologies de la Sante du Quebec (Canada)	www.cets.gouv.qc.ca
National Information Centre of Health Services Research and Health Care Technology (USA)	http://www.nlm.nih.gov/nichsr/nichsr.html
Finnish Office for Health Technology Assessment (FinOHTA) (Finland)	http://www.stakes.fi/finohta/linkit/
Institute Medical Technology Assessment (Netherlands)	http://www.bmg.eur.nl/imta/
AETS (Spain)	http://www.isciii.es/unidad/aet/cdoc.htm
Agence Nationale d'Accreditation et d'Evaluation en Sante (France)	www.anaes.fr

Eligibility criteria for studies

The search strategy retrieved a total of 1,663 non-duplicate citations. The citations were screened by one reviewer to determine eligibility using the criteria outlined in Table 7. A representative sample of 501 citations (30%) was independently assessed by a second reviewer. Agreement between reviewers was 0.70 (kappa statistic). All potentially eligible articles identified using this screening process were retrieved and both reviewers independently assessed all retrieved articles for eligibility and quality. Discrepancies in the results of this eligibility assessment were resolved by discussion.

Table 7 Study exclusion criteria

1. Not a clinical study Non-systematic reviews, case reports, case series, studies of less than 20 patients, letters, editorials, animal, in-vitro and laboratory studies will be excluded. Only comparative primary studies will be eligible for inclusion. 2. Wrong patient group Studies were to include patients with early localised prostate cancer staged as T1 or T2, with a Gleason score of ≤6, and a PSA≤10. At least 85% of patients must meet these criteria for a study to be considered eligible for inclusion. 3. Wrong intervention Studies were to use brachytherapy with I 125 permanent implants. Studies will not be excluded if ≥50% of the sample receives I 125 and the remainder receives Pd 103 (or other implant types). Studies combining brachytherapy with EBRT in some patients will be excluded unless data can be disaggregated. 4. Wrong comparator Studies were to use radical prostatectomy, external beam radiation therapy, or no initial treatment or deferred treatment ("active surveillance") as comparators. 5. Wrong outcomes Studies had to report on at least one of the following: • survival; • progression; • quality of life; • safety; or • costs. 6. Not in English Only studies available in English were eligible for inclusion.

Based on these criteria, 1,646 papers (99%) were excluded from this review.

Five health technology reports and eight published systematic reviews were identified in the search and fulfilled the inclusion criteria for the review. The HTA reports were published by the NHS R&D Health Technology Assessment Programme (Hummel, Paisley, Morgan et al 2003), the Agency for Healthcare Research and Quality (Harris, Lohr, Beck et al 2002), The Wessex Institute for Health Research and Development (Patterson 2001), the *Conseil d'Evaluation des Technologies de la Sante du Quebec* (CETS, 2000), and the Alberta Heritage Foundation for Medical Research (Wills and Hailey 1999). No RCTs were found. Four comparative, non-randomised cohort studies that met the inclusion criteria were identified. One of these studies, published in 1999, was also included in the previous MSAC assessment (Zelefsky, Wallner, Ling et al 1999). However, the direct comparisons between brachytherapy and a comparator treatment made by this study in terms of safety and effectiveness were not reported in the previous review. Hence, in systematically reviewing the literature from 1999 onwards, this study was considered eligible for inclusion in the current assessment.

The QUORUM flowchart (Figure 1) summarises the results of the literature search and the application of the study exclusion criteria.

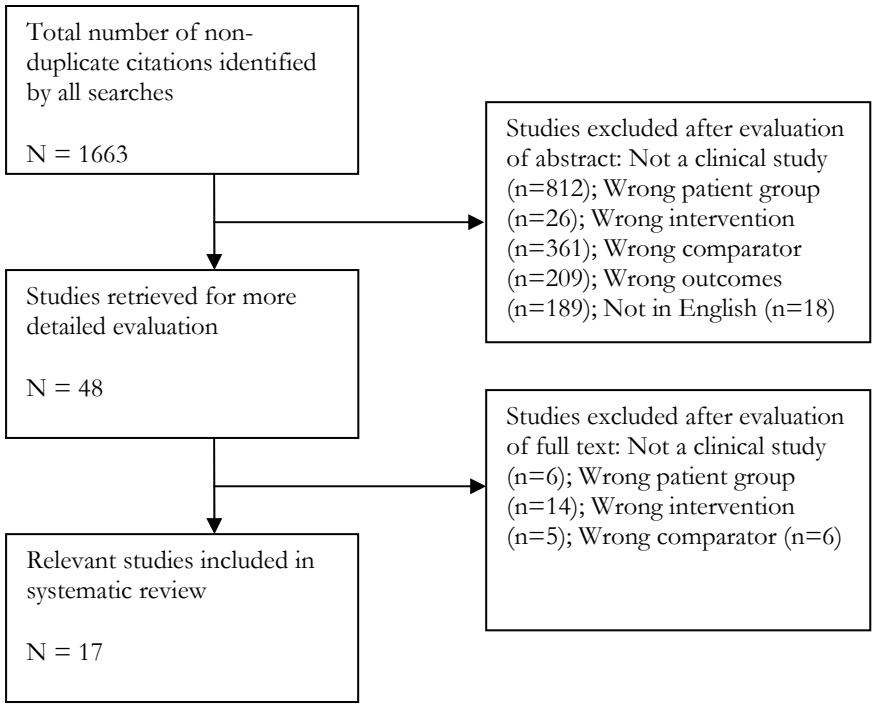


Figure 1 QUORUM flowchart of study inclusions and exclusions

Appraisal

Assessment of eligible 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 8) 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 require expert clinical input as part of its determination.

Table 8 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 9.

The three subdomains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 9.

Table 9 Designations of levels of evidence[a]

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant RCTs
II	Evidence obtained from at least one properly-designed RCT
III-1	Evidence obtained from well-designed pseudoRCTs (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

a Modified from NHMRC 1999.

Quality appraisal tools

Study quality refers to the extent to which the methods used within the chosen study design are adequate to avoid potential bias. A structured appraisal to assess the quality of all included studies was performed. A standard checklist for quality appraisal of non-randomised controlled studies is given in Table 10.

Table 10 Checklist for appraising the quality of studies of interventions[a]

1.	Were subjects selected prospectively or retrospectively?
2.	Was the intervention reliably ascertained?
3.	Was there sufficient description about how the subjects were selected for the new intervention and comparison groups?
4.	Was there sufficient description about the distribution of prognostic factors for the new intervention and comparison groups? Were the groups comparable for these factors?
5.	Did the study adequately control for potential confounding factors in the design or analysis?
6.	Was the measurement of outcomes unbiased (ie blinded to treatment group and comparable across groups)?
7.	Was follow-up long enough for outcomes to occur?
8.	What proportion of the cohort was followed-up and were there exclusions from the analysis?
9.	Were drop-out rates and reasons for drop-out similar across intervention and unexposed groups?

a Adapted from Khan, ter Riet, Popay et al 2001.

Data extraction

Data were extracted using a standardised instrument designed for this review. Data extraction was performed independently by two reviewers and any discrepancies were resolved by discussion or a third reviewer if required. The data extraction tables are provided in Appendix C.

Expert advice

An Advisory Panel with expertise in urology, radiation oncology and consumer issues was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for Advisory Panels, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the Advisory Panel is provided at Appendix B.

Results of assessment

Is it safe?

The literature search identified 12 systematic reviews and two primary studies examining adverse events and quality of life outcomes for patients receiving brachytherapy for the treatment of prostate cancer. Ten of the systematic reviews and both primary studies (Borchers, Kirschner-Hermanns, Brehmer et al 2004; Zelefsky, Wallner, Ling et al 1999) reported effectiveness data as well as adverse events or quality of life, and are discussed in further detail in the section titled 'Is it effective?'. Of the two systematic reviews that only addressed questions of safety and quality of life, one described quality of life following brachytherapy with or without EBRT, RP, and EBRT alone for the treatment of early prostate cancer, and included none of the primary studies reported in the current review (Henderson, Laing & Langley 2004). The other reported on a meta-analysis comparing rates of erectile function after brachytherapy with or without EBRT, standard or nerve-sparing RP, and cryotherapy, and could not be assessed in terms of the overlap of included studies with the present assessment (Robinson, Moritz & Fung 2002). None of the systematic reviews or primary studies compared brachytherapy with active surveillance in terms of morbidity or quality of life. Observational studies comparing the physical, sexual and emotional function of patients receiving treatments for early prostate cancer to those without prostate cancer provide some relevant information about the potential impact of treatment (for example, Joly, Brune, Couette et al 1998).

Three systematic reviews based comparisons of complications between treatments on a single study or systematic review addressing safety. In one review (Nilsson, Norlen & Widmark 2004), the included study did not meet the eligibility criteria for the current assessment in terms of the implant type and patient group, and hence the safety conclusions of this review are not discussed. Two reviews (Norderhaug, Dahl, Hoisaeter et al 2003; Wilt 2003) included a single primary study or systematic review that also met the eligibility criteria for this assessment. Hence, discussion is based on these studies or reviews (Zelefsky, Wallner, Ling et al 1999; Harris, Lohr, Beck et al 2002) rather than on the systematic reviews addressing them. One further review (Patterson 2001) included a study ineligible for the current assessment due to using the wrong implant type (Fulmer, Bissonette, Petroni et al 2001), as well as a systematic review that was eligible for inclusion in this review (Wills and Hailey 1999). Therefore, the safety conclusions of Wills and Hailey are discussed, while the review conducted by Patterson is not.

The results and conclusions of the included studies for the outcomes of erectile, urinary and bowel function are discussed in the following sections. These outcomes are recommended by the American Brachytherapy Society as critical for reporting morbidity after prostate brachytherapy (Nag, Ellis, Merrick et al 2002). In some cases, these domains are encompassed by an overall measure of quality of life, and these results are also discussed.

Sexual function

Systematic reviews

Seven systematic reviews investigated the impact of brachytherapy on post-treatment sexual functioning. Four of these reviews found that brachytherapy resulted in higher sexual function compared with other treatments. The meta-analysis reported by Robinson, Moritz & Fung (2002) found that the probability of maintaining erectile function at approximately one year after treatment was significantly greater for patients treated with brachytherapy (76%) than those treated with EBRT (55%), nerve-sparing RP (34%) or standard RP (25%) ($p<0.05$). Age adjusted one-year probabilities were 80 per cent for brachytherapy, 68 per cent for EBRT, 22 per cent for nerve-sparing RP, and 16 per cent for standard RP. However, it is noted that erectile function may not stabilise until two years after treatment. Brachytherapy was unable to be compared with the other treatment modalities at two years. Furthermore, for the included studies the implant type or types, and patient characteristics in terms of pretreatment stage, Gleason score and PSA could not be determined from the paper.

The systematic review conducted by Henderson, Laing & Langley (2004) included studies measuring sexual functioning with instruments such as the FACT-P, UCLA-PCI, and EPIC. It was concluded that trends in studies to date suggest that patients undergoing brachytherapy, particularly without androgen deprivation, have better sexual function than patients who receive EBRT or RP. Similarly, Doust, Miller, Duchesne et al (2004) concluded that brachytherapy generally resulted in lower rates of impotence than EBRT and RP, although this finding was not consistent across all included studies. Furthermore, a review conducted by the Conseil d'Evaluation des Technologies de la Sante du Quebec (CETS, 2000) observed that rates of impotence from brachytherapy series ranged from 0 to 34 per cent, lower than the 57 per cent reported for RP in a previous systematic review.

An additional review conducted by Wills and Hailey (1999) concluded that few studies comment on impotence after brachytherapy, but rates vary considerably for those that do. Based on the comparative study by Zelefsky, Wallner, Ling et al (1999) and comparisons with other series addressing impotence after EBRT or RP, it was concluded that brachytherapy resulted in equivalent or fewer side-effects.

One systematic review reported mixed evidence, or evidence for worse sexual function after brachytherapy than for other treatments. Hummel, Paisley, Morgan et al (2003) note that although case series are consistent with previous reviews noting no differences between brachytherapy and standard treatments, evidence from matched case-control studies show worse sexual function than standard treatments.

A further review estimated rates of sexual complications after brachytherapy but did not attempt to compare these with other treatments. Harris, Lohr, Beck et al (2002) estimated that 36 per cent of men will have some erectile dysfunction one year after brachytherapy.

Primary studies

Both primary studies addressed sexual functioning. A prospective comparative cohort study conducted by Borchers, Kirschner-Hermanns, Brehmer et al (2004) reported changes in health related quality of life (HRQoL) (based on questions from the EPRTC-

QLQ-C30) from pretreatment levels at 6 and 12 months after brachytherapy, standard RP, and nerve-sparing RP. Domains considered in the HRQoL assessment were physical, role, emotional, cognitive, social and sexual functioning, as well as a global HRQoL score. Borchers, Kirschner-Hermanns, Brehmer et al (2004) report that sexual functioning was the only domain for which significant changes occurred between baseline and 12 months post-treatment. Sexual functioning included questions relating to a change for the worse in functioning, reduced sexual activity, loss of sexual pleasure, loss of sexual satisfaction, and quality of erection. Significant decreases in sexual functioning occurred in the standard RP and nerve-sparing RP groups, but no significant change was evident in the brachytherapy group. Sexual functioning declined to a significantly greater extent in the standard RP group than the brachytherapy group (p=0.015).

In a retrospective comparative cohort study comparing morbidity after brachytherapy and 3DCRT, Zelefsky, Wallner, Ling et al (1999) found no differences in terms of the five-year actuarial likelihood of erectile dysfunction in initially potent patients after brachytherapy (53%) and 3DCRT (43%) (p=0.52).

Urinary function

Systematic reviews

Six systematic reviews described urinary function after brachytherapy treatment. Reviews generally report that brachytherapy may result in higher rates of continence than other treatments, but other symptoms such as obstruction and irritation may be worse. Henderson, Laing & Langley (2004) reviewed studies measuring urinary functioning with instruments such as the FACT-P, UCLA-PCI, EPIC, and IPSS. It is noted that incontinence is greatest for RP in most of the relevant literature. However, problems with storage or voiding have been reported following brachytherapy, and the reported superiority of brachytherapy over RP in terms of incontinence may be an artefact of these symptoms not being included in the urinary subscale of the UCLA-PCI. Similarly, Doust, Miller, Duchesne et al (2004) found that brachytherapy may have some advantage over RP and EBRT in terms of urinary continence, but has a higher incidence of short-term obstructive and irritative urinary symptoms.

Crook, Lukka, Klotz et al (2001) found acute urinary symptoms (irritative or obstructive symptoms requiring drug treatment, urinary retention) to be more prolonged and severe with brachytherapy than EBRT, but the basis for this comparison is unclear.

Wills and Hailey (1999) concluded that brachytherapy resulted in equivalent or fewer urinary side-effects than EBRT or RP, with rates of incontinence generally being below 6 per cent for all treatment modalities. Comparisons were based on the study by Zelefsky, Wallner, Ling et al (1999), and comparisons of brachytherapy series and other series addressing EBRT or RP. Similarly, the CETS review (2000) found that rates of incontinence in brachytherapy series are no worse (or, for the case of men with no history of TURP, are actually better) than those reported in a previous systematic review for RP.

The systematic review by Hummel, Paisley, Morgan et al (2003) reported mixed evidence. Case series are consistent with a conclusion of no differences between brachytherapy and

standard treatments; however, evidence from matched case-control studies show worse urinary symptoms than standard treatments compared with healthy controls.

One review estimated rates of urinary complications after brachytherapy but did not attempt to compare these with other treatments. Harris, Lohr, Beck et al (2002) estimated that 2 to 12 per cent of men will have some urinary symptoms one year after brachytherapy.

Primary studies

Both primary studies reported on urinary function after brachytherapy. Zelefsky, Wallner, Ling et al (1999) reported a higher five-year actuarial likelihood of late grade 3 urinary toxicity (urethral stricture) in brachytherapy patients (12%) than in 3DCRT patients (2%) (p=0.0002). Borchers, Kirschner-Hermanns, Brehmer et al (2004) reported that the rate of urinary incontinence (as measured by the EPRTC-QLQ-C30 prostate cancer module) at one year after treatment was significantly lower for brachytherapy (13%) than for standard RP (62%) and nerve-sparing RP (39%) (Pearson's chi square test, p<0.0001 calculated from table percentages provided). There were no statistically significant differences in the rates of urinary urgency or bother between patients receiving brachytherapy and those receiving standard RP or nerve-sparing RP (Pearson's chi square test calculated from table percentages provided).

Bowel / rectal function

Systematic reviews

Five reviews addressed bowel functioning after treatment with brachytherapy. Three of these reviews report worse bowel function after brachytherapy than comparator treatments. Henderson, Laing & Langley (2004) report that the literature generally shows bowel function following brachytherapy to be worse than after RP; however, several primary studies included in the review did not separate brachytherapy patients from those undergoing brachytherapy with EBRT. Bowel function was assessed by the UCLA-PCI and EPIC instruments in the included studies. Hummel, Paisley, Morgan et al (2003) reported that matched case-control studies show worse bowel function with brachytherapy than standard treatments. The CETS review (2000) found higher rates of proctitis in brachytherapy series than in RP series, but lower than in conventional EBRT series.

One review (Wills and Hailey, 1999) concluded that brachytherapy resulted in equivalent or fewer gastrointestinal (GI) side-effects than EBRT or RP, with rates of GI complications generally being below 5 per cent for all treatment modalities. Comparisons were based on the study by Zelefsky, Wallner, Ling et al (1999), and comparisons of brachytherapy series and other series addressing EBRT or RP.

An additional review estimated rates of bowel dysfunction after brachytherapy but did not attempt to compare these with other treatments. Harris, Lohr, Beck et al (2002) estimated that 18 per cent of men will have some bowel dysfunction one year after brachytherapy.

Primary studies

Both primary studies reported on bowel function after brachytherapy. Zelefsky, Wallner, Ling et al (1999) found no significant difference in the five-year actuarial likelihood of late grade 2 rectal toxicity following brachytherapy (11%) or 3DCRT (6%) (p=0.71). Borchers, Kirschner-Hermanns, Brehmer et al (2004) reported that the rate of stool incontinence (as measured by the EPRTC-QLQ-C30 prostate cancer module) at one year after treatment was significantly higher for brachytherapy (20%) compared with standard RP (5%) and nerve-sparing RP (4%) (Pearson's chi square test, p=0.03 calculated from table percentages provided).

General quality of life

Systematic reviews

Two systematic reviews examined general quality of life. Henderson, Laing & Langley's (2003) review of the quality of life literature concluded that in general, the majority of men undergoing brachytherapy, RP or EBRT report normal or near normal general HRQoL, both in the first year after treatment and at further follow-up. Included studies used a range of quality of life tools, including RAND SF36, TAG Life/Family, FACT-P, UCLA-PCI, EPIC, and IPSS. However, this conclusion appears to be based on a single study that was ineligible for inclusion in the present review due to the study population included, and in which the analysis did not separate brachytherapy from other forms of radiotherapy.

Similarly, Hummel, Paisley, Morgan et al (2003) concluded that general HRQoL after brachytherapy has been shown to be comparable both to standard treatments and to age-matched healthy controls. Included studies used the following quality of life tools: RAND SF36, TAG Life/Family, FACT-P, FACT-G, UCLA-PCI, EPIC, EORTC QLQ C30, and the Nottingham Health Profile. However, the conclusions regarding general HRQoL were based on two studies ineligible for consideration in the current assessment (one due to the patient group included in the study, the other for examining brachytherapy in combination with EBRT). These studies compared brachtherapy (with and without EBRT) to RP.

Primary studies

A single prospective comparative cohort study examined overall quality of life. Borchers, Kirschner-Hermanns, Brehmer et al (2004) measured changes in overall HRQoL (based on questions from the EPRTC-QLQ-C30) from pretreatment levels to those at 6 and 12 months after brachytherapy, standard RP, and nerve-sparing RP. No significant differences in HRQoL were observed when brachytherapy was compared with either standard RP or RP with nerve-sparing at 12 months.

Conclusions

Sexual function: Brachytherapy appears to be comparable to or better than RP and EBRT in terms of sexual functioning after treatment. This conclusion is based on two level III-2 studies, one showing better outcomes at one year for brachytherapy compared with standard RP as determined by a global sexual functioning measure (p=0.015) (Borchers, Kirschner-Hermanns, Brehmer et al 2004), the other reporting no difference

in five year actuarial likelihood of erectile dysfunction between brachytherapy and 3DCRT (p=0.52) (Zelefsky, Wallner, Ling et al 1999). These general conclusions are supported by five level III-2 systematic reviews reporting the comparability or superiority of a variety of brachytherapy interventions in comparison with other treatments in broader patient groups than considered here. There is insufficient evidence to allow comparisons between brachytherapy and active surveillance at this time.

Urinary function: In terms of post-treatment urinary continence, brachytherapy appears to have a lower rate of incontinence than RP. However, brachytherapy may result in higher rates of irritative or obstructive symptoms than EBRT. This conclusion is based on two level III-2 studies, one showing lower rates of incontinence one year after brachytherapy than after standard RP or nerve-sparing RP (p<0.0001) (Borchers, Kirschner-Hermanns, Brehmer et al 2004), the other reporting significantly higher five-year actuarial likelihood of urethral stricture after brachytherapy compared with 3DCRT (p=0.0002) (Zelefsky, Wallner, Ling et al 1999). These general conclusions are supported by four level III-2 systematic reviews reporting the relative advantage of a variety of brachytherapy interventions in terms of continence and/or disadvantage in terms of obstructive or irritative symptoms in comparison with other treatments in broader patient groups than considered here. There is insufficient evidence to allow comparisons between brachytherapy and active surveillance at this time.

Bowel/rectal function: Brachytherapy may result in worse bowel/rectal functioning in terms of stool incontinence after treatment than RP. Brachytherapy may be comparable to EBRT in terms of post-treatment bowel/rectal functioning as measured by grade 2 rectal toxicity. This conclusion is based on two level III-2 studies, one showing higher rates of stool incontinence one year after brachytherapy than after standard RP or nerve-sparing RP (p=0.03) (Borchers, Kirschner-Hermanns, Brehmer et al 2004), the other reporting no difference in the five-year actuarial likelihood of late grade 2 rectal toxicity after brachytherapy compared with 3DCRT (p=0.71) (Zelefsky, Wallner, Ling et al 1999). Five level III-2 systematic reviews reported disparate conclusions regarding the relative advantage, disadvantage or comparability of a variety of brachytherapy interventions in terms of bowel/rectal function in comparison with other treatments and in broader patient groups than considered here. There is insufficient evidence to allow comparisons between brachytherapy and active surveillance at this time.

General quality of life: Overall quality of life at one year after treatment appears to be comparable for brachytherapy and RP. This conclusion is based on one level III-2 study showing no significant differences in HRQoL between brachytherapy, standard RP or nerve-sparing RP one year after treatment (p=0.74) (Borchers, Kirschner-Hermanns, Brehmer et al 2004). This general conclusion is supported by two level III-2 systematic reviews reporting the comparability of a variety of brachytherapy interventions in comparison with RP in broader patient groups than considered here. There is insufficient evidence to compare brachytherapy with EBRT and active surveillance at this time.

Strength of evidence: Uncertainty exists surrounding these results. The primary studies were not of high quality in terms of study design, the reporting of patient selection criteria, and the comparability of baseline characteristics between treatment groups. There was also variability between the studies in the delivery of treatment (adjuvant or neoadjuvant androgen ablation, brachytherapy dose), and the length of follow-up. Additionally, the studies used different measures of the various safety domains, and compared brachytherapy with different treatments. Such quality and heterogeneity issues limit the comparability of the studies, and the certainty of conclusions that may be

derived from them. These issues are addressed in more depth in the following section ('Is it effective?'). Similarly, the systematic reviews addressing morbidity and quality of life are of variable quality, and apply to the intervention and population of interest to this assessment to varying degrees (again, discussed further in the following section). As a result, the conclusions of these reviews are not always consistent with one another. Hence, the preceding conclusions should be interpreted with caution. Conclusions regarding bowel/rectal function should be approached with particular caution, given the absence of converging conclusions from previous systematic reviews.

The collection of data from patients receiving brachytherapy in routine clinical practice is critical in defining rates of adverse events in Australia. Ideally, these data could be interpreted together with data collected from other patients receiving comparator treatments.

Is it effective?

Systematic reviews and HTAs

Eleven systematic reviews of variable quality were identified that addressed the effectiveness of brachytherapy. Four reviews included evidence from RCTs, seven included observational studies that compared brachytherapy with other treatments and seven provided a summary of case series. Three reviews provided sufficient information to meet all the specified criteria for high quality reviews (Harris, Lohr, Beck et al 2002; Hummel, Paisley, Morgan et al 2003; Norderhaug, Dahl, Hoisaeter et al 2003). Furthermore, three reviews did not include primary studies or other systematic reviews that have been included in the current assessment (Harris, Lohr, Beck et al 2002; CETS 2000; Crook, Lukka, Klotz et al 2001). The remaining eight reviews, to varying degrees, based their conclusions on other studies or reviews included here. One such review (Doust, Miller, Duchesne et al 2004) updated the previous MSAC assessment of brachytherapy for prostate cancer by extending the search period by two years.

No review included in the following discussion addressed I 125 implants specifically, but rather assessed multiple implant types (various combinations of I 125 and Pd 103, Au 198, or Ir 192). Reviews also varied in the degree to which the population of interest to the current review was specifically addressed. None of the reviews attempted a statistical synthesis of effectiveness data due to varying characteristics of the primary studies. Table 11 describes the populations, implant types, effectiveness outcomes addressed, and quality characteristics of the systematic reviews. Each review is discussed in detail in the following sections.

Hummel, Paisley, Morgan et al (2003)

This high quality review assessed new interventions for early localised prostate cancer (stages T1 and T2). Brachytherapy was one modality evaluated, and included studies that compared brachytherapy with RP, EBRT or compared different brachytherapy interventions. A total of 24 studies were identified, including four systematic reviews, 2 RCTs, 4 cohort or case control studies, 1 study comparing times/places with or without the intervention, and 13 case series. A number of studies (including the two RCTs) compared different brachytherapy impant types (I 125 vs Pd 103), and hence will not be considered here. Included studies used I 125 implants along with other radioisotope

types (Pd 103, high dose rate Ir 192, low dose temporary I-192), and studies combining brachytherapy and EBRT were not excluded. Furthermore, studies were included if less than or equal to 50 per cent of patients were staged T3 or higher, and there were no patient eligibility criteria relating to Gleason's score or pretreatment PSA. Gleason and PSA characteristics varied greatly between and within studies.

The authors noted that very few studies met the eligibility criteria of the review, and the majority of those that did were case series of variable quality. However, it was concluded that there is some evidence to suggest that brachytherapy performs as well as standard treatments (RP and EBRT) in terms of bDFS for lower risk patients.

Crook, Lukka, Klotz et al (2001)

This review assessed permanent seed brachytherapy performed under ultrasound or CT guidance in patients with T1 or T2 disease. Although no comparators were specified, Crook, Lukka, Klotz et al (2001) concluded that for patients staged T1c or T2a with Gleason scores of less than or equal to 6 and PSA less than or equal to 10, brachytherapy and RP are equivalent in terms of biological no evidence of disease (bNED). However, this conclusion appears to be based on a single cohort study comparing Pd 103 implants with RP and EBRT (D'Amico, Whittington, Malkowicz et al 1998).

Doust, Miller, Duchesne et al (2004)

Doust, Miller, Duchesne et al (2004) updated the previous MSAC assessment of brachytherapy compared with RP and EBRT by extending the search period by two years to June 2002. The review identified two systematic reviews, seven retrospective cohort studies and 22 case series assessing survival rates following brachytherapy. In 23 studies, overlapping or duplicate cohorts of patients were reported. Implants were not restricted to I 125. No eligibility criteria were enforced relating to the population of interest in terms of pretreatment stage, Gleason score or PSA; however, conclusions were made regarding the patient group of interest in the present review. It was concluded that for patients with low risk disease (T1 or T2, Gleason ≤ 6, and PSA ≤ 10) survival rates are generally high for brachytherapy, EBRT and RP (>90%), and the modalities appear to have similar effectiveness. There was insufficient evidence to compare brachytherapy to active surveillance.

Norderhaug, Dahl, Hoisaeter et al (2003)

This review compared brachytherapy with RP, EBRT, EBRT plus brachytherapy boost, and watchful waiting (active surveillance). The review question addressed brachytherapy in general, hence included studies used Pd 103 and Ir-92 implants as well as I 125. Furthermore, the review question did not focus on early prostate cancer, and hence did not exclude studies assessing the effectiveness of brachytherapy in higher risk patients.

One good quality case series study was identified that compared I 125 brachytherapy with RP. This study also compared I 125 brachytherapy with EBRT. In addition, one good quality cohort study and one good quality case control study were identified which compared either I 125 or Pd 103 brachytherapy with EBRT. No RCTs were identified, and no studies were presented comparing brachytherapy with active surveillance. It was concluded that the evidence for the clinical effectiveness of prostate brachytherapy was generally poor. Brachytherapy was comparable to RP and EBRT in terms of cancer

Table 11 Populations, implant types, effectiveness outcomes addressed, and quality characteristics of the included systematic reviews

Study	Included studies	Patients	Implants	Comparators	Outcomes	Quality
Hummel, Paisley, Morgan et al (2003)	24 studies SR (4) RCT (2) Obs (5) CS (13)	Early localised prostate cancer Stage: T1 and T2. Papers excluded where >50% of patients T3 or more.	I 125, Pd 103, high dose rate Ir 192, low dose temporary I-192. Monotherapy and in combination with EBRT with or without androgen deprivation.	EBRT RP Different brachytherapy interventions	Clinical and biochemical disease-free survival.	High quality.
Crook, Lukka, Klotz et al (2001)	15 studies Obs (3) CS (13)	Clinically localised prostate cancer. Stage: T1 and T2.	I 125, Pd 103	Not defined.	bNED. Biopsy results.	Only two databases were searched. Validity of included studies not assessed.
Doust, Miller, Duchesne et al (2004)	67 studies SR (2) RCT (1) Obs (15) CS (49)	Localised prostate cancer. Staging not defined.	Not stated. (Assume I 125 and Pd 103 based on previous MSAC assessment).	EBRT RP	No biochemical or clinical evidence of disease.	Validity of studies assessed but not described. Insufficient details of included studies presented.
Norderhaug, Dahl, Hoisaeter et al (2003)	5 studies Obs (5)	Prostate cancer. Staging not defined.	I 125, Pd 103, Ir 192.	EBRT RP Active surveillance	bNED.	High quality.
Nilsson, Norlen & Widmark (2004)	39 studies RCT (2) Non-RCT (37)	Prostate cancer. Staging not defined.	I 125 or Pd 103, with or without EBRT.	EBRT RP	Failure-free survival, bDFS, recurrence-free survival.	Only two databases were searched. Validity of included studies assessed but criteria not described.
Wilt (2003)	4 studies SR (3) RCT (1)	Clinically localised prostate cancer. Staging not defined.	Not stated (included studies assessed I 125, Pd 103, Au 198).	EBRT RP	Evidence of disease measured by PSA.	Search strategy not described. Validity of included studies assessed but criteria not described. Insufficient details of included studies presented.
Harris, Lohr, Beck et al (2002)	9 studies (for brachytherapy question) CS (9)	Prostate cancer. Staging not defined.	I 125, Au 198.	EBRT RP Androgen deprivation Active surveillance	Survival.	High quality.

Table 11 Populations, implant types, effectiveness outcomes addressed, and quality characteristics of the included systematic reviews, continued from previous page

Study	Included studies	Patients	Implants	Comparators	Outcomes	Quality
Wills and Hailey (1999)	23 studies Study designs not described in detail.	Prostate cancer. Staging not defined.	I 125, Pd 103.	RP EBRT 3DCRT Brachytherapy + hormone therapy Brachytherapy + EBRT	Biochemical control, clinical control, survival.	Inclusion criteria not stated.
Patterson (2001)	3 studies SR (1) Obs (2)	Localised prostate cancer. Staging not defined.	I 125, Pd 103, with or without EBRT.	EBRT RP Drug treatments Active surveillance	Failure-free survival.	Inclusion criteria and search strategy not presented. Insufficient detail about included studies.
CETS (2000)	33 studies Obs (3) CS (30)	Prostate cancer. Staging not defined.	I 125, Pd 103, Au 198, high dose rate Ir 192.	RP EBRT	Freedom from clinical or biochemical failure.	Only one database was searched. Search strategy not described.
Quaranta , Marks and Anscher (2004)	23 studies Study designs not described in detail.	Low risk prostate cancer (T1–T2a, Gleason score ≤6, PSA ≤10).	Not stated (included studies assessed I 125 and Pd 103).	RP	bDFS.	Only one database was searched. Search strategy not described. Validity of included studies assessed but criteria not described.

Abbreviations: bDFS—biochemical Disease-free survival; bNED—biological no evidence of disease; 3DCRT—three-dimensional conformal radiation therapy; CS—case series; EBRT—external beam radiation therapy; Obs—observational study; PSA—prostate specific antigen; RP—radical prostatectomy; RCT—randomised controlled trials; SR—systematic reviews.

control—there was no evidence for differences between the modalities in terms of 5- to 10-year disease-free survival based on PSA measures.

Nilsson, Norlen & Widmark (2004)

Nilsson, Norlen & Widmark (2004) conducted a systematic review of the effects of radiation therapy (including brachytherapy) in prostate cancer. The brachytherapy interventions assessed included I 125 or Pd 103 seeds with or without additional EBRT. Some studies described in the review also included patients with higher risk profiles in terms of pretreatment clinical stage, Gleason score or PSA. Two RCTs (addressing I 125 vs Pd 103, and hence not considered here) and 37 non-randomised studies were included in the review. No comparators were specified, but five included studies compared brachytherapy with RP or EBRT. The review concluded that for patients of low risk (PSA <10, T0-T2a, Gleason ≤ 6), TRUS-guided permanent-seed brachytherapy appears to have similar long-term (>5 years) treatment outcomes to RP and 3DCRT.

Wilt (2003)

Wilt (2003) conducted a systematic review addressing the effects of treatments (including brachytherapy) for clinically localised (T0–T2) prostate cancer. The search found no RCTs addressing this question for brachytherapy. Instead, three systematic reviews (also included in the present assessment) and one retrospective cohort study were identified. On the basis of these studies, it was noted that the results of brachytherapy, RP and EBRT were similar for men with T1 or T2 tumours, Gleason less than or equal to 6, and PSA less than or equal to 10.

Harris, Lohr, Beck et al (2002)

This review conducted a comprehensive search to determine the efficacy of brachytherapy in the context of a broader review of the effects of prostate cancer screening. Citations were included if they described an RCT or a large cohort with control group, follow-up was at least two years, at least 75 per cent of patients were followed, and health outcomes were reported. No RCTs were identified that compared brachytherapy with any other treatment. Two observational studies (one using I 125, the other Au 198) were identified, but it was concluded that the efficacy of brachytherapy for clinically localised prostate cancer remains unknown.

The authors also attempted to compare any active treatment with active surveillance. They identified two RCTs comparing prostatectomy and hormonal treatment with active surveillance, four retrospective cohort studies and a pooled analysis of six other cohort studies. Methodological problems with the two RCTs and selection biases in the observational studies limited the interpretation of these results. It was concluded that there was no strong RCT evidence to support a difference in the effectiveness of active treatment versus surveillance for clinically localised prostate cancer and that men with well-differentiated, clinically localised prostate cancer experienced little or no reduction in survival compared with similar men without prostate cancer.

Wills and Hailey (1999)

In order to assess the effectiveness of brachytherapy for prostate cancer, this comprehensive systematic review identified three studies comparing biochemical control of brachytherapy with RP, EBRT and 3DCRT, while a further two series compared results of RP with an unrelated brachytherapy series (23 studies were included in the whole review). No comparative studies of clinical control or survival were identified. Studies assessing both I 125 and Pd 103 implants were included in the review, and no eligibility criteria (including those addressing the patient group or groups of interest) were stated. The authors concluded that brachytherapy appears promising in the short term, but its potential for influencing overall outcomes (particularly long-term morbidity and survival) are unknown. Alternative treatments are continuing to evolve so that the safety and efficacy of brachytherapy relative to these is uncertain and may continue to change. Hence, it was noted that the choice of treatment should continue to be made based on physician and patient preference rather than scientific evidence of the superiority of a particular treatment modality.

Patterson (2001)

Patterson (2001) reviewed the literature to determine the effects of brachytherapy versus other radiotherapy, RP, watchful waiting or drug therapies for the treatment of localised prostate cancer. One systematic review and two cohort studies (three papers) were

included. It was concluded that valid comparisons between brachytherapy and other treatments are not possible based on the evidence identified, and that the effectiveness of brachytherapy will remain uncertain until RCTs are conducted.

CETS (2000)

The Conseil d'Evaluation des Technologies de la Sante du Quebec (CETS 2000) review summarises the evidence of brachytherapy's intended and unintended effects and compares these to other current treatments. The review identified 33 articles, 3 of which were comparative (brachytherapy vs RP or EBRT) and reported pre- and post-treatment PSA information. The remainder were case series with or without PSA information. Included studies used a variety of implant types. Based on the literature identified, the authors concluded that it is not possible to demonstrate an efficacy advantage of brachytherapy over other treatments, nor is it possible to exclude the possibility that brachytherapy is less efficacious.

Quaranta, Marks and Anscher (2004)

This review compared results from large brachytherapy and RP series in terms of five-year bDFS. Studies were only included if they reported PSA-based outcomes, the total number of patients was at least 100, median follow-up was at least three years, and patients could be stratified according to the pretreatment prognostic factors of stage, Gleason score and PSA. Quaranta, Marks and Ancher's (2004) findings in relation to patients of low risk (T1–T2a, Gleason ≤6, PSA ≤10) are relevant to the present assessment. Thirteen brachytherapy series and 10 RP series addressing the low risk group were included. A weighted average five-year bNED was calculated for the brachytherapy series (87.4%). The five-year bNED reported in the RP series ranged from 68 to 100 per cent. It was concluded that excellent results were reported with both modalities, and that there is no evidence supporting the superiority of one treatment over the other.

Conclusions

Evidence from 11 systematic reviews, including 3 reviews of high quality, suggests that outcomes in terms of disease progression are similar for brachytherapy, RP and EBRT. High quality evidence about long-term patient survival was not identified.

The strength of this evidence is limited by the variation in characteristics of the primary studies and in the quality of the methods and reporting of the systematic reviews themselves. The relevance of the included studies to the research question specified for this review also varied and thus evidence from eligible primary studies presented in the following sections provide the most applicable evidence for this assessment.

None of the four reviews that attempted to compare brachytherapy with active surveillance identified studies that directly compared these two options (Harris, Lohr, Beck et al 2002; Norderhaug, Dahl, Hoisaeter et al 2003; Patterson 2001, Wilt 2003). Two reviews also attempted to compare any active treatment with active surveillance. Harris, Lohr, Beck et al (2002) concluded that existing RCT evidence was not conclusive for men with early localised disease. Wilt (2003) referred exclusively to the results of this review.

Primary studies

The literature review identified four comparative cohort studies published from 1999 onwards that addressed the effectiveness of brachytherapy compared with RP and EBRT (including 3DCRT). No RCTs with published results compared the effectiveness of brachytherapy with RP, EBRT or active surveillance. One ongoing RCT comparing brachytherapy with RP was identified (SPIRIT) (Langley, Henderson & Laing 2004); however, this trial has subsequently been discontinued due to slow patient accrual. No studies were identified that compared brachytherapy with active surveillance.

Among the four included primary studies, none were reported as prospective, although it appears that patients were recruited prospectively in Borchers, Kirschner-Hermanns, Brehmer et al (2004), where consecutive patients were selected from an existing QoL study. Ciezki, Klein, Angermeier et al (2004) and Stokes (2000) are reported as retrospective studies, and while Zelefsky, Wallner, Ling et al (1999) does not report how patients were recruited, it appears that it is a retrospective study. While three studies reported their inclusion criteria, there was either limited or no description of how the type of treatment was selected for patients.

Baseline characteristics are available separately for each treatment group in three of the four studies. In two of these studies, most baseline characteristics were similar between treatment groups; however, in Zelefsky, Wallner, Ling et al (1999) the proportions of patients with stage T1c disease and those who were potent before treatment were statistically greater for brachytherapy. While baseline characteristics are presented in Ciezki, Klein, Angermeier et al (2004), they are not presented separately for each therapy and as such the comparability of patients at baseline is not known. Follow-up was variable between the studies, with two reporting a minimum follow-up of less than two years (Zelefsky, Wallner, Ling et al 1999; Borchers, Kirschner-Hermanns, Brehmer et al 2004).

Variability between the included studies was evident in the provision of adjuvant or neoadjuvant androgen deprivation therapy, patients' pretreatment prostate volume, the prescribed brachytherapy radiation dose (140–160 Gy), definitions of failure or relapse, and the methods used to determine the timing of failure or relapse. Characteristics and results of the studies are summarised in Table 12. The studies are described in further detail in the following sections.

Table 12 Patients, implant types, comparators, results and quality characteristics of the included primary studies

Study	*N*	Patients	Implants	Comparators	Results	Quality
Stokes (2000)	147 low risk (540 total)	T1c or T2a Gleason ≤6 PSA ≤10	I 125	EBRT RP	5 yr bDFS:[a] —Brachytherapy = 78% —EBRT = 85% —RP = 78% —(no statistical comparison)	Retrospective. Data extracted from separate survival curves.
Borchers, Kirschner-Hermanns, Brehmer et al (2004)	132 low risk (132 total)	T1–T2a Gleason ≤6 PSA ≤10	I 125	RP RP + NS	bRFS: —Brachytherapy = 85% —RP = 96% (p=0.04) —Median follow-up 27 months Survival: —Brachytherapy = 1 death at 6 mo from MI —RP = no deaths	Prospective? Min follow-up <2 yrs. Proportion of pts followed up and exclusions not reported. Histopathology upstaged 18% of pts to T3, and 28% to Gleason score of 7.
Ciezki, Klein, Angermeier et al (2004)	1,074 low risk (1668 total)	T1–T2c Gleason ≤6 PSA ≤10	I 125	EBRT RP	5 yr bRFS: —Brachytherapy = 90% —EBRT = 90% —RP = 89% —(p=0.82)	Retrospective. Inclusion criteria not described. Baseline comparability of treatment groups unknown. Implant type not mentioned in article text (determined from keywords).
Zelefsky, Wallner, Ling et al (1999)	282 low risk (282 total)	T1–T2b Gleason ≤6 PSA ≤10	I 125	3DCRT	5 yr bRFS:[a] —Brachytherapy = 82% —3DCRT = 88% —(p=0.09).	Retrospective. Significantly more T1 pts in brachytherapy than in 3DCRT group. Min follow-up <2 yrs (6mo for brachytherapy group).

Abbreviations: bDFS/bRFS—biochemical disease/relapse-free survival; EBRT—external beam radiation therapy; MI—myocardial infarction; NS—nerve-sparing; PSA—prostate specific antigen; RP—radical prostatectomy.

a Actuarial survival data; this is an alternative method for the calculation of the survival curves based on the 'actuarial assumption' about the average number of individuals at risk during a time interval allowing for censoring.

Stokes (2000)

This retrospective, non-randomised cohort study examined bDFS in patients undergoing I 125 seed placement, RP or EBRT. Between 1988 and 1994, 585 patients were diagnosed with organ-confined carcinoma of the prostate. Those who were assessed as surgical candidates underwent surgery. Those who were not surgical candidates or who declined surgery were referred for I 125 brachytherapy (those staged T1 or T2, with prostate volume < 50 cm^3, Gleason Score ≤6, PSA <50 and no significant obstructive symptoms) or EBRT (those staged T1 to T3).

Surgery consisted of pelvic lymphadenectomy and retropubic RP. Brachytherapy involved ultrasound-guided permanent I 125 seed implantation to deliver a minimum prostatic dose of 160 Gy. (The American Association of Physics in Medicine Task Group 43 (TG-43) reported a new formalism for calculating brachytherapy dosimetry in 1995

(Rivard, Coursey, DeWerd et al 2004). This means that the dosimetric characteristics of studies such as Stokes (2000) which recruited patients prior to 1995 may not be directly comparable to studies which recruited patients after this time). No brachytherapy patients received neoadjuvant androgen ablation. EBRT was delivered prior to the availability of 3DCRT, and consisted of a 4500 cGy dose, boosted at 180 to 200 cGy fractions to a final target dose of 6500 to 7000 cGy. No EBRT patients received neoadjuvant or concurrent androgen ablation treatment.

Patients were followed up with serial PSA levels and digital exams at minimum 3 to 6 month intervals for between 2 and 10 years post-treatment, with a mean of 5 years 8 months for brachytherapy, 6 years 1 month for EBRT, and 6 years 5 months for RP. Surgical patients were considered biochemical failures if they had consistent detectable PSA (>0.2 ng/mL), three consecutive PSA increases at minimum three month intervals, or substantial PSA increase warranting androgen ablation or pelvic irradiation. Brachytherapy and EBRT patients were considered biochemical failures if their nadir PSA at one year was greater than or equal to 1, or if patients with a nadir PSA of less than 1 at one year had three subsequent consecutive PSA increases. The date of first PSA increase was used as the date of biochemical failure.

A total of 234 patients underwent RP, with 12 excluded from the study due to death from intercurrent disease or being lost to follow-up, leaving 222 analysable patients. Two hundred and three patients underwent I 125, with 17 excluded, leaving 186 brachytherapy patients included in the study. Of the 148 patients undergoing EBRT, 16 were excluded, leaving 132 evaluable patients.

Patients were retrospectively stratified into low (T1c–T2a, Gleason score ≤6, PSA ≤10), intermediate (T2b, Gleason score ≤6, PSA=10-20), or high (T2c–T3, Gleason score ≥7, PSA >20) risk groups. Only patients classified as low risk are eligible for inclusion in the present assessment. Of the 147 low risk patients, 72 underwent brachytherapy, 21 underwent EBRT, and 54 underwent RP. Brachytherapy and RP appeared to have similar five-year rates of bDFS (78%). EBRT appeared to have slightly higher five-year bDFS (85%), although this is based on a small number of patients undergoing EBRT. These data were extracted from separate survival curves and thus did not allow statistical comparisons.

Borchers, Kirschner-Hermanns, Brehmer et al (2004)

In a prospective, consecutive non-randomised cohort, Borchers, Kirschner-Hermanns, Brehmer et al (2004) examined PSA relapse-free survival in patients undergoing I 125 seed placement, RP or nerve-sparing RP. Patients were selected from a quality of life study initiated in 1999 which included 374 with histologically confirmed prostate cancer. Consecutive patients with a clinical stage of T1 to T2N0M0, Gleason score of less than 7, PSA less than or equal to 10, a prostate volume of less than or equal to 60 mL, and tumours localised to one lobe on sextant biopsy were included. A total of 132 consecutive patients were entered into the study.

Fifty-two patients with a urinary flow rate greater than 10mL/s and no significant residual urine were selected for brachytherapy. I 125 seeds were implanted under general or regional anaesthesia using a perineal template-guided peripheral loading technique, using TRUS. TRUS images at 5 mm increments were taken prior to implantation. The prescription dose was 145 Gy, with a median of 54 seeds implanted. For those undergoing surgery not considered for potency, an extended RP was carried out, always

contralateral to the nerve-sparing procedure. A total of 42 patients underwent RP. Thirty-eight patients who underwent nerve-sparing RP were also included in the study. Clinical and histopathological characteristics were similar in all treatment groups, except the RP and nerve-sparing RP groups, which were significantly younger. No neoadjuvant therapy was permitted for any patients.

PSA relapse for the RP groups was defined as an increase in serum PSA to greater than 0.1 ng/mL. For the brachytherapy group, PSA relapse was defined as three consecutive PSA rises at three month intervals. The determination of timing of PSA relapse was not discussed. The median follow-up was 26 months, with a range of 12 to 60 months. PSA relapse-free survival was significantly higher in the RP group (96%; 95% CI 91–100) than in the brachytherapy group (85%; 95% CI 74–95) (p=0.04). It is unclear whether this result refers to all RP patients or only to those without nerve-sparing. It is also noted that PSA relapse may occur more than 5 years after treatment, and hence a median follow-up of 26 months may be insufficient.

One patient died six months following brachytherapy from a myocardial infarction. There were no deaths following RP.

Ciezki, Klein, Angermeier et al (2004)

Ciezki, Klein, Angermeier et al (2004) examined a large, retrospective, non-randomised cohort to compare brachytherapy with RP and EBRT, with and without androgen ablation. Between 1996 and 2001, 1668 patients with low or intermediate risk prostate cancer were treated definitively with brachytherapy (n=386), RP (n=519) or EBRT (n=763). Only those patients categorised as being at low risk (T1–T2, Gleason score ≤6, PSA ≤10) were eligible for inclusion in the present review. Of 1,074 low risk patients, 295 underwent brachytherapy, 282 had EBRT and 497 had RP.

Patients receiving brachytherapy were treated with a radiation dose of 144 Gy using I 125 seeds (I 125 was not specifically described in the paper, but was included as a keyword). The median radiation dose for EBRT was 78 Gy. Androgen deprivation was included as part of treatment for 22 per cent of the brachytherapy group, 15.2 per cent of the EBRT group, and 9.5 per cent of the RP group, for a median duration of 6, 6, and 3 months, respectively (duration was calculated based on the whole cohort).

Patients were followed up between 24 and 94 months post-treatment, with a mean of 48 months. Surgical patients were considered biochemical failures if they had PSA greater than 0.5 ng/mL. Biochemical failure was defined by the American Society for Therapeutic Radiation and Oncology consensus (three consecutive PSA increases at either three or four month intervals) for brachytherapy and EBRT patients. The method used to determine of the date of biochemical failure was not presented.

Five-year biological relapse-free survival rates were found to be similar for brachytherapy (90%), EBRT (90%), and RP (89%) (p=0.82).

Zelefsky, Wallner, Ling et al (1999)

This retrospective, non-randomised cohort study examined actuarial PSA relapse-free survival in patients undergoing I 125 brachytherapy or 3DCRT. Between 1988 and 1995, 743 patients with clinically localised adenocarcinoma of the prostate were treated with 3DCRT with photon beams. A total of 137 were characterised as having favourable

prognostic features (T0–T2 disease, Gleason score ≤6, PSA ≤10), and were included in the analysis. Between 1988 and 1997, 245 patients were treated with CT planned prostate brachytherapy, of whom 145 had favourable prognostic features and were included in the study. Clinical and biochemical characteristics of the brachytherapy and 3DCRT groups were similar, apart from significantly fewer T1c patients and patients who were potent pretreatment in the 3DCRT group.

Brachytherapy with I 125 seeds was conducted with pretreatment CT and computer optimisation of needle placement and with fluoroscopic monitoring during the procedure. Ultrasound was not used routinely. The prescribed minimum radiation dose was 140 to 160 Gy (however, recruitment appears to have occurred prior to the introduction of the TG-43 formalism, and hence dosimetry for this study may not be directly comparable with later studies). Neoadjuvant androgen deprivation was given in 11 per cent of brachytherapy patients for a median of 2 months prior to treatment. Patients undergoing 3DCRT were treated with 6 individually shaped coplanar fields, delivered with 15 to 25 MV x-rays in daily fractions of 1.8 Gy. The prescribed radiation dose was 64.8 Gy (n=21), 70.2 Gy (n=54), 75.6 Gy (n=59), and 81.0 Gy (n=3). Neoadjuvant androgen deprivation was given in 17 per cent of patients three months prior to treatment, then continuing until radiotherapy was completed.

Follow-up evaluations were performed at one and four months, and then six-monthly. The median follow-up in the 3DCRT group was 36 months (range 12 to 109 months); the median follow-up in the brachytherapy group was 24 months (range 6 to 103 months). PSA relapse was defined as three consecutive PSA elevations from the post-treatment nadir value. The date of relapse was calculated as the mid-point between PSA nadir and the first PSA elevation.

Similar five-year actuarial PSA relapse-free survival rates were found for brachytherapy (82%) and 3DCRT (88%) (p=0.09).

Conclusions

In addition to the evidence available from the systematic reviews described previously, four observational studies provide Level III-2 evidence eligible for this assessment.

Survival: There is insufficient evidence to compare survival rates between brachytherapy, RP, EBRT and active surveillance.

Progression: One eligible study observed a modest statistically significant advantage in relapse free survival for radical prostatectomy compared to brachytherapy (Borchers, Kirschner-Hermanns, Brehmer et al 2004); however, this advantage was not observed in two other studies. The authors of this study reported that histopathological results from the RP groups upgraded initial staging and Gleason scores such that 18 per cent had extraprostatic tumours (≥T3) and 28 per cent had a Gleason score of 7, indicating a substantial proportion of included patients were of higher risk than those eligible for inclusion in this review (Borchers, Kirschner-Hermanns, Brehmer et al 2004).

No evidence was identified for a direct comparison of disease progression in patients treated with brachytherapy or active surveillance.

Overall, the available evidence does not demonstrate a difference in survival or disease progression between brachytherapy, RP and EBRT at this time. However, the strength of

this evidence is not high. It is possible that the studies reviewed are not large enough (insufficiently powered) or that the study timeframes are too short to detect true clinically significant differences between treatments. Two studies (Borchers, Kirschner-Hermanns, Brehmer et al 2004; Zelefsky, Wallner, Ling et al 1999) reported a minimum follow-up period of less than two years, the minimum recommended for the publication of PSA results in clinical trials (Cox, Grignon, Kaplan et al 1997). Given that the studies are non-randomised and the criteria for selection of patients to each treatment type are largely unknown it is also possible that study bias may obscure the true relative effects of these treatments.

Furthermore, variation between the characteristics of included studies in the provision of neoadjuvant or adjuvant androgen deprivation therapy, pretreatment prostate volume, the definitions used for treatment failure, and the methods used to determine the timing of treatment failure preclude the synthesis of this evidence.

Prospective trials are required to draw more definitive conclusions about the relative effect (or non-inferiority) of treatment. The SPIRIT trial comparing brachytherapy with RP was ongoing at the time of the literature search, but this trial has subsequently been discontinued due to slow patient accrual.

What are the economic considerations?

Economic evaluation compares the expected cost and effects of alternative therapies in a defined treatment population. A search of the literature was conducted for economic evaluations of prostate brachytherapy, including the NHS Economic Evaluation Database and the Harvard Cost-Effectiveness Analysis Registry. The only previous Australian economic analysis found was the estimation of direct costs for brachytherapy, RP and EBRT procedures undertaken in the previous MSAC assessment (2000). These costs have been updated, and are presented in Table 13. This table presents a best estimate of direct costs. It does not take into account follow-up costs associated with treating health states and in particular adverse events from alternative therapies.

Table 13 Estimated costs: brachytherapy, radical prostatectomy and EBRT (estimated to nearest A$)

	Brachytherapy	Radical prostatectomy	EBRT
Total medical costs [a]	14,050	10,137	9,266

a Includes, where applicable, general costs (eg. TRUS, planning CT, health program grant, operating theatre costs), theatre staff (eg. urologist, radiation oncologist/medical physicist, anaesthetist, surgical assistance), and disposables (eg. iodine seeds, implant needles, pharmacy).

Table 13 differs from the estimate of direct costs previously undertaken by MSAC (2000) in a number of ways. Firstly, the costs attached to the urologist, radiation oncologist and anaesthetist MBS item numbers are derived from average fees billed in 2004 rather than the fees reimbursed by Medicare. In the case of the urologist fee for RP, this has been calculated as an average over three applicable items, weighted by the proportion of services provided under each item. The surgical assistance cost has been calculated as one-fifth of this weighted average as specified in the MBS. Secondly, the average fees for anaesthetist services also include the average fees charged for the time components of the procedures, as well as other modifiers such as the age of the patient. Thirdly, the Australian Government's Health Program Grant for EBRT has been included in the direct costs. Finally, it was the expert opinion of the Advisory Panel that physiotherapy was not conducted after RP in this patient group, and hence this cost was removed.

The differences in costs described in Table 13 can be interpreted as the incremental cost of therapy if it is assumed that there are no differences between treatments in terms of their effectiveness and the rates of adverse events. While the present systematic review has found no evidence for differences in treatment effect between the therapies, the treatments do in fact appear to have different side-effect profiles. If this difference in adverse events rates is accepted then modelling of costs and modelling of QALYs clearly needs to take these differences into account. It is inadequate both in estimating effects and costs to ignore these differences where they exist. If costs do not allow for costs of follow-up treatment they can misrepresent the incremental costs of alternative therapies.

A high quality cost-effectiveness evaluation undertaken as part of a systematic review by Hummel, Paisley, Morgan et al (2003) for the National Institute of Clinical Excellence in the United Kingdom was identified which included expected effects and costs associated with treating adverse events. This systematic review modelled the effects of differences in adverse events rates on QALYs of these alternative therapies in a population of males aged 65 years with moderately differentiated tumours assuming no survival differences between active therapies. This assumption of no survival effect has also been supported in the current review. The adverse event rates, utilities associated with these adverse events and modelled QALYs based on these rates and weights are presented in tables 14, 15 and 16.

Table 14 Adverse event incidence rates by treatment

Therapy	Impotence	Urinary symptoms	Bowel Injury
Active surveillance	0	0	0
Radical prostatectomy	0.58	0.15	0
External beam radiation	0.31	0.20	0.15
Brachytherapy	0.18	0.14	0.03

Table 15 Utilities by potential outcome

Outcome	Utilities
Active surveillance	0.73
Radical treatment no side-effects	0.78
Impotence	0.70
Incontinence	0.60
Bowel injury	0.47

Table 16 QALYs by therapy—patients aged 65 years with moderately differentiated tumours

Therapy	QALYs	Incremental QALYs versus active surveillance
Active surveillance	7.52	
Radical prostatectomy	7.78	0.26
External beam radiation	7.47	-0.05
Brachytherapy	8.07	0.55

Additional evidence since the UK systematic review (Hummel, Paisley, Morgan et al 2003) from a cohort study (Borchers, Kirschner-Hermanns, Brehmer et al 2004) suggests that brachytherapy may have a higher adverse event rate for bowel/rectal dysfuntion than that modelled in Table 14. In general, the use of different measures of bowel/rectal

dysfunction between such studies creates uncertainty about the relative rates across therapies. In addition, the relative utility weights applied to adverse events in the UK study in Table 15 may not necessarily have been seen as reflecting those of decision makers in this MSAC review in an Australian setting.

Hummel, Paisley, Morgan et al (2003) modelled costs of alternative therapies in the United Kingdom allowing for direct costs and costs of follow-up using the same model and assumptions used in estimating QALYs. Purchase power parity conversion of these UK costs to Australia are presented in Appendix E (OECD 2003). These costs may not, however, be transferable from the United Kingdom to Australia due to differences in relative prices and practice. For example, in considering differences in practice between the United Kingdom and Australia, brachytherpy is performed by radiologists, medical oncologists and medical physicists in the United Kingdom.

In modelling incremental cost-effectiveness of the alternative therapies current evidence from Australia and the United Kingdom is clearly inadequate. Costs of therapy modelled in the United Kingdom are likely to bias relative costs of therapies due to differences in relative prices and practice and the suggestion that the rate of adverse events for bowel/rectal dysfunction with brachytherpay may have been underestimated (Borchers, Kirschner-Hermanns, Brehmer et al 2004). Using Australian evidence of direct costs of therapy ignores the cost of follow-up treatment (effectively assuming no treatment effect). While this is likely to bias incremental costs of brachytherapy upwards (given evidence of lower adverse event rates than alternative therapies and consequently lower treatment costs of follow-up), the shortages of medical physicists in Australia also needs to be taken into account.

If evidence of effects from the UK study is directly translated to Australia, then the effects of alternative therapies are expected as indicated in Table 17.

Table 17 Incremental cost and QALYs for treatment versus active surveillance

Therapy	Incremental QALYs
Radical prostatectomy	0.26
External beam radiation	-0.05
Brachytherapy	0.55
Active surveillance	0

Sensitivity analyses

One-way sensitivity analyses were conducted to ascertain the sensitivity of results to variations in the baseline assumptions on the effects of brachytherapy. Table 18 presents one-way sensitivity analysis allowing for uncertainty in estimating QALYs.

Applying incremental QALY estimates for brachytherapy versus active surveillance under a best case scenario for brachytherapy results in 0.73 QALYs gained. However, in a worst case scenario, brachytherapy has lower QALYs than active surveillance, RP and EBRT. Estimates of cost per QALY saved are therefore highly sensitive to differences in QALY estimations, highlighting the need for further research into survival and quality of life effects.

Table 18 Sensitivity analyses applying incremental QALY estimates for brachytherapy versus active surveillance

	Incremental QALYs
Upper bound	0.73
Lower bound	-0.08

Conclusions

Conclusions about the cost-effectiveness of brachytherapy relative to EBRT, RP and active surveillance are limited by the lack of data on relative effects and costs associated with the effects of these procedures. A comparison of the direct costs for each procedure is only helpful if we assume that there is no difference in outcomes between these procedures. If this assumption is made, then from evidence in Table 13, brachytherapy is expected to be more expensive than other therapies and would be dominated by these therapies. Although this review has not identified evidence of difference in survival across therapies, evidence of differences in adverse event rates suggest that the relative costs and effects of these events need to be taken into account. Modelling of effects based on QALYs from the United Kingdom (Hummel, Paisley, Morgan et al 2003) suggests brachytherapy may have a gain in QALYs relative to other therapies. However, this gain is highly sensitive to modelling, with brachytherapy less effective than each of the other strategies in a worst case scenario. Evidence of potentially higher adverse event rates for bowel dysfunction reported by Borchers, Kirschner-Hermanns, Brehmer et al (2004) reinforces this uncertainty. This highlights the need for further research into comparative treatment effects in terms of both adverse events and survival before conclusive recommendations can be made about the relative effects or cost-effectiveness of brachytherapy.

Future economic evaluation of brachytherapy should also consider the potential for higher costs associated with the use of brachytherapy in a wider population than is currently treated. The limited number of medical physicists is likely to lead to higher economic costs than have been modelled in Australia, and further evidence is required to adequately inform decision making. There are also clearly labour workforce implications if utilisation of brachytherapy were to be expanded.

Conclusions

Safety

Findings from two cohort studies (level III-2 evidence) indicate that brachytherapy is comparable to or better than RP and EBRT in terms of sexual functioning after treatment. These studies also showed a relative advantage for brachytherapy over RP in terms of rates of post-treatment continence. However brachytherapy may result in higher rates of irritative or obstructive urinary symptoms than EBRT.

One study reported that brachytherapy may result in worse bowel/rectal functioning in terms of stool incontinence after treatment than RP (level III-2 evidence). Another study reported that brachytherapy may be comparable to EBRT in terms of post-treatment bowel/rectal functioning as measured by grade 2 rectal toxicity (level III-2 evidence).

Limited evidence also compared overall quality of life between brachytherapy and comparators for patients with early localised prostate cancer. One cohort study indicated that quality of life at one year after treatment appears to be comparable for brachytherapy and RP (level III-2 evidence).

The findings of systematic reviews of case series (level III-2 evidence) are generally consistent with the preceding conclusions, except for the domain of bowel/rectal functioning, where systematic reviews report disparate conclusions regarding the relative advantage, disadvantage or comparability of brachytherapy compared with other treatments.

Effectiveness

Ten level III-2 systematic reviews and four level III-2 primary studies provided effectiveness information. Evidence from primary studies was considered the most appropriate in drawing conclusions regarding effectiveness. The systematic reviews provided supporting evidence.

Overall, the available evidence does not demonstrate a difference in survival or disease progression between brachytherapy, RP and EBRT at this time. No primary studies or systematic reviews were identified that compared survival rates between brachytherapy, RP, EBRT and active surveillance. One eligible study observed a modest statistically significant advantage in relapse free survival for radical prostatectomy compared to brachytherapy (Borchers, Kirschner-Hermanns, Brehmer et al 2004); however, histopathological results from the RP groups upgraded initial staging and Gleason scores such that a substantial proportion of included patients were of higher risk than those eligible for inclusion in this review (Borchers, Kirschner-Hermanns, Brehmer et al 2004). The advantage reported in this study was not observed in two other studies. All included systematic reviews concluded that a difference in disease progression between brachytherapy, RP and EBRT could not be demonstrated.

No evidence was identified for a direct comparison of disease progression in patients treated with brachytherapy or active surveillance. One review (and another referencing

this review) compared any active treatment with active surveillance, and concluded that RCTs in this area were not conclusive.

Issues in the interpretation of evidence

The strength of this evidence is not high. It is possible that the studies reviewed are not large enough (insufficiently powered) or that the study timeframes are too short to detect true clinically significant differences between treatments. Two studies (Borchers, Kirschner-Hermanns, Brehmer et al 2004; Zelefsky, Wallner, Ling et al 1999) reported a minimum follow-up period of less than two years, the minimum recommended for the publication of PSA results in clinical trials (Cox, Grignon, Kaplan et al 1997). Given that the studies are non-randomised and the criteria for selection of patients to each treatment type are largely unknown it is also possible that study bias may obscure the true relative effects of these treatments.

Furthermore, variation between the characteristics of included studies in the provision of neoadjuvant or adjuvant androgen deprivation therapy, pretreatment prostate volume, measurement of safety and treatment failure, and comparators used preclude the synthesis of this evidence.

The strength of the evidence provided by the systematic reviews is limited by the variation in characteristics of the primary studies and in the quality of the methods and reporting of the systematic reviews themselves. The relevance of the reviews to the research question specified for this assessment also varied considerably in terms of the implant types assessed and the populations studied. As a result, the conclusions of these reviews are not always consistent with one another. Hence, the preceding conclusions should be interpreted with caution. Conclusions regarding bowel/rectal function should be approached with particular caution, given the absence of converging conclusions from previous systematic reviews.

Prospective trials are required to draw more definitive conclusions about the relative effect (or non-inferiority) of treatment. The SPIRIT trial comparing brachytherapy with RP was undertaken in 2002, but this trial has subsequently been discontinued due to slow patient accrual.

Cost-effectiveness

Direct costs of brachytherpy treatment relative to RP and ERBT have been estimated for an Australian setting, with the expected costs of brachytherapy ($14,050) higher than RP ($10,137) or ERBT ($9,266). These costs do not, however, include costs of follow-up treatment. While this review and a previous a National Institute of Clinical Excellence review (Hummel, Paisley, Morgan et al 2003) found no evidence for treatment effects on survival, evidence suggests differences in adverse events rates. Modelling of expected QALYs allowing for differences in adverse event rates in 65-year-old patients with moderately differentiated tumours, Hummel, Paisley, Morgan et al (2003) suggest brachytherapy has higher expected QALYs (8.02) than RP (7.78), EBRT (7.47) or active surveillance (7.52). This gain in QALYs is, however, highly sensitive to modelled adverse event rates, with brachytherapy less effective than each of the other strategies in a worst case scenario. This uncertainty is further reinforced by suggestions of higher rates of bowel dysfunction than modelled by Hummel, Paisley, Morgan et al. Further research

into comparative treatment effects on adverse events as well as survival is required before conclusive recommendations can be made about the effects, costs or cost-effectiveness of strategies.

Recommendation

Following a reassessment of further evidence pertaining to the safety, effectiveness and cost-effectiveness of brachytherapy for the treatment of prostate cancer, interim public funding should continue for patients with prostate cancer meeting the following criteria:

- at clinical stages T1 and T2 with Gleason scores of less than or equal to 6, prostate specific antigen (PSA) of less than or equal to 10ng/ml, gland volume less than 40 cc and with life expectancy of more than 10 years; and

- where the treatment is conducted at approved sites.

- The Minister for Health and Ageing accepted this recommendation on 28 November 2005.

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of MSAC comprises 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**
Dr Stephen Blamey (Chair)	general surgery
Associate Professor John Atherton	cardiology
Professor Syd Bell	pathology
Dr Michael Cleary	emergency medicine
Dr Paul Craft	clinical epidemiology and oncology
Dr Gerry FitzGerald	Australian Health Ministers' Advisory Council representative
Dr Kwun Fong	thoracic medicine
Dr Debra Graves	medical administrator
Professor Jane Hall	health economics
Professor John Horvath	Chief Medical Officer, Department of Health and Ageing
Ms Rosemary Huxtable	Department of Health and Ageing representative
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Associate Professor Donald Perry-Keene	endocrinology
Dr Ray Kirk	health research

Dr Michael Kitchener	nuclear medicine
Professor Alan Lopez	medical statistics and population health
Dr Ewa Piejko	general practice
Ms Sheila Rimmer	consumer health issues
Professor Jeffrey Robinson	obstetrics and gynaecology
Professor Michael Solomon	colorectal surgery, clinical epidemiology
Professor Ken Thomson	radiology
Dr Douglas Travis	urology

Appendix B Advisory Panel

Advisory Panel for MSAC application 1089
Brachytherapy for the treatment of prostate cancer

Dr Michael Kitchener (Chair) MBBS FRACP Senior Visiting Nuclear Physician The Queen Elizabeth Hospital Adelaide, SA	member of MSAC
Dr Ross Cartmill MBBS FRACS FRCS Senior Visiting Urologist Princess Alexandra Hospital Brisbane, Qld	co-opted urologist
Mr Clive Deverall AM Hon Litt Consumer Representative National Cancer Strategies Group & Research Committee NH&MRC Perth, WA	co-opted Consumers' Health Forum of Australia
Dr Graeme Dickie Cancer Care Services Royal Brisbane & Women's Hospital Herston, Qld	co-opted radiation oncologist
Professor Gillian Duchesne BSc MB ChB MD FRCR FRANZCR Director of Radiation Oncology Peter MacCallum Cancer Centre Melbourne, Vic	co-opted radiation oncologist
Dr Alastair Tulloch Perth, WA	co-opted urological surgeon
Evaluators Mr Luke Marinovich Dr Sarah Lord Ms Alison Griffiths Dr Simon Eckermann	NHMRC Clinical Trials Centre
Department of Health and Ageing Ms Brenda Campe Project Manager	Health Technology Section

HTA reports/systematic reviews			
Author & year	Databases searched & search strategy	Inclusion & quality criteria	Quality assessment of review
Hummel, Paisley, Morgan et al (2003)	Searched Premedline, Medline, Embase, Biological Abstracts, CCTR, CDSR, Cinahl, EBM Reviews—ACP Journal Club, Health Economic Evaluations Database, Health Information management Consortium, NHS DARE, NHS EED, NHS HTA, Science Citation Index, and Social Sciences Citation Index for the period 1992-2003. Manual searches of retrieved citation performed. Information also obtained from 30 additional sources including the Agency for Healthcare Research and Quality (USA), Bandolier, Cancer Research UK, Centre for Health Economics (York), Health Services Research Unit (Aberdeen), INAHTA, National Cancer Institute (USA), National Guidelines Clearinghouse, Prostate Cancer Research Institute (USA), and the Royal Pharmaceutical Society. Search terms: prostate neoplasms, neoplasms, carcinoma, adenocarcinoma, prostatic diseases, prostate, cancer, malignant, brachytherapy, interstitial irradiation, transperineal interstitial permanent prostate brachytherapy.	Study design: NHMRC level I to level IV evidence was included in the review, case series with *n*<100 and follow-up <5 yrs excluded. Patients: Early localised prostate cancer (stages T1 and T2). Papers excluded where >50% of patients T3 or more. Interventions: Partly predefined, partly identified though search. Included brachytherapy, NHT, AHT, hormone monotherapy, 3DCRT, IMRT, cryotherapy, HIFU, IMTT, RITA, laser phocoagulation, gene therapy, high linear energy transfer radiation, radionuclide therapy, and vaccine therapy. Comparators: Not predefined. Included studies compared brachytherapy with EBRT, RP, or different brachytherapy interventions. Outcomes: Survival, QoL, cost-effectiveness. Quality criteria: No formal quality assessment. Application of methods: Iterative search and inclusion/exclusion process to establish what constitutes 'new and emerging' technologies. No language or study/publication type restrictions applied to main searches, except Social Science Citation Index limited to English. Low quality evidence included unless sufficient high quality evidence (RCT) identified. Where a majority of evidence was low quality (case series), sample size/follow-up cut-offs were developed and applied. Data extracted into pro forma by a single reviewer.	Were inclusion/exclusion criteria reported that addressed the review question? —Yes. Was the search adequate? —Yes. Was the validity of the included studies assessed? —Study limitations are discussed qualitatively. Are sufficient details about the individual included studies presented? —Yes. Studies addressing I 125 were not considered separately from other implant types, hence conclusions do not relate specifically to I 125. Studies were included if ≤50% of patients T3 or more, and there were no patient eligibility criteria relating to Gleason's score or pretreatment PSA. Gleason and PSA characteristics varied greatly between and within studies. Hence, some presented studies do not fit eligibility criteria for this review.
	Results		
	Results for brachytherapy only are presented. 24 studies were included (4 systematic reviews, 2 RCTS, 4 cohort or case control studies, 1 study comparing times/places with/without intervention, 13 case series). The authors concluded that there is some evidence to suggest that brachytherapy performs as well as standard treatments (RP and EBRT) in terms of bDFS for lower risk patients, although worse for intermediate and high risk patients. Evidence in terms of complications is mixed, with case series evidence reporting lower rates of complications than standard treatments, and cohort/case control evidence of lower disease-specific QoL but similar general QoL compared with standard treatments.		

HTA reports/systematic reviews			
Author & year	Databases searched & search strategy	Inclusion & quality criteria	Quality assessment of review
Crook, Lukka, Klotz et al (2001)	Searched Medline and Cancerlit from 1988 to 1999. Search terms: prostate cancer, prostate neoplasm, brachytherapy, seed implant, interstitial radiotherapy, practice guideline, meta-analysis, randomised clinical trial, clinical trial.	Study design: NHMRC level III to level IV evidence was included in the review. Patients: Clinically localised prostate cancer (stages T1 and T2). Interventions: Permanent seed brachytherapy performed under ultrasound or CT guidance. Comparators: Not specified. Outcomes: Freedom from biochemical failure (bNED), biopsy results or toxicity. Quality criteria: Not specified. Application of methods: Evidence selected and reviewed by a single reviewer. Draft evidence summary discussed and agreed by group consensus.	Were inclusion/exclusion criteria reported that addressed the review question? —Yes. Was the search adequate? —Only two databases were searched. Hand searching or retrieval of information from other sources was not reported. Was the validity of the included studies assessed? —No. Are sufficient details about the individual included studies presented? —Yes. Studies addressing I 125 were not considered separately from other implant types, hence conclusions do not relate specifically to I 125. There were no patient eligibility criteria relating to Gleason's score or pretreatment PSA. Hence, some presented studies do not fit eligibility criteria for this review.
	Results		
	15 studies were included (3 cohort studies, 13 case series). There were no RCTs. bNED stated to be equivalent for brachytherapy and RP in pts with T1c or T2a, Gleason ≤ 6, and PSA ≤ 10, although this appears to be based on a single cohort study comparing Pd 103 implants with RP and EBRT. Acute (<12 mo) adverse events included irritative urinary symptoms (46–54%), urinary retention (1–14%), and proctitis (1–2%). Chronic (>12 mo) adverse events included ≥ grade 2 urinary symptoms (29% at 12 mo, 14% at 24 mo), incontinence (5–6%), incontinence after TURP (13%), hematuria (1–2%), stricture (1–2%0, proctitis (1–3%), and impotence (4–14%). The authors concluded that there is insufficient evidence to recommend the use of brachytherapy over current standard therapy for localised prostate cancer, however it should be available for selected patients (T1c or T2a, Gleason ≤ 6, PSA ≤ 10).		

HTA reports/systematic reviews			
Author & year	Databases searched & search strategy	Inclusion & quality criteria	Quality assessment of review
Doust, Miller, Duchesne et al (2004)	Searched CCRCT, Medline, Embase and Cancerlit from Jan 1990 to June 2002. Search terms: prostate cancer, prostate neoplasm, brachytherapy, iodine implant, prostate implant.	Study design: NHMRC level III to level IV evidence was included in the review. Patients: Localised prostate cancer. Interventions: Permanent seed brachytherapy. Excluded studies of combination EBRT. Comparators: Not prespecified. Included studies compared brachytherapy with EBRT or RP. Outcomes: Effectiveness and safety. Quality criteria: Not prespecified. Application of methods: Studies with ≤40 pts excluded. Studies assessed for quality and data extracted independently by two reviewers, with disagreement resolved by consensus.	Were inclusion/exclusion criteria reported that addressed the review question? —Yes. Was the search adequate? —Yes. Was the validity of the included studies assessed? —Yes, but not described. Are sufficient details about the individual included studies presented? —No. Studies addressing I 125 were not considered separately from other implant types, hence conclusions do not relate specifically to I 125. There were no patient eligibility criteria relating to Gleason's score or pretreatment PSA. Hence, some presented studies do not fit eligibility criteria for this review. This review extends the previous MSAC assessment by two years.
	Results		
	67 studies were included (2 systematic reviews, 1 RCT, 1 prospective cohort study, 14 retrospective cohort studies, 49 case series). For patients with low risk disease (T1 or T2, Gleason ≤ 6, and PSA ≤ 10) survival rates are generally high for brachytherapy, EBRT and RP (>90%). Incidence of complications appears to be similar for brachytherapy, EBRT, and RP. Brachytherapy may have higher preservation of potency and urinary continence, but a higher incidence of obstructive and irritative urinary symptoms, at least in the short term. The authors concluded that low risk patients should be advised to make treatment decisions based on side-effects profiles.		

HTA reports/systematic reviews			
Author & year	Databases searched & search strategy	Inclusion & quality criteria	Quality assessment of review
Norderhaug, Dahl, Hoisaeter et al (2003)	Searched HTA database and Cochrane Library. Also Medline and Embase (Jan 2000 to Aug 2001). Information was also obtained from current controlled trials, National Cancer Institute, and National Research Register. Search terms: prostate, brachytherapy, seed, internal, implant.	Study design: NHMRC level III evidence was included in the review. Patients: Prostate cancer. Interventions: Brachytherapy. Comparators: RP, EBRT, watchful waiting. Outcomes: Tumour control, treatment associated complications, cost-effectiveness. Quality criteria: Studies scored 1 for RCTs; 2 for controlled trials, cohort or case control studies; and 3 for patient series and cross-sectional studies. Validity scores of very good, good, or poor based on comparability of groups with respect to age, disease severity, comorbidity, and time and number of patients followed. Poor studies were excluded. Application of methods: No information regarding application of methods.	Were inclusion/exclusion criteria reported that addressed the review question? —Yes. Was the search adequate? —Yes. Was the validity of the included studies assessed? —Yes. Are sufficient details about the individual included studies presented? —Yes. Studies addressing I 125 were not considered separately from other implant types, hence conclusions do not relate specifically to I 125. There were no patient eligibility criteria relating to Gleason's score or pretreatment PSA. Hence, some presented studies do not fit eligibility criteria for this review.
	Results		
	5 cohort or case-control studies were included. The authors concluded that there was no evidence for any difference between brachytherapy, EBRT and RP in 5- to 10-yr disease-free survival based on PSA measures. There was no evidence that short-term complications after brachytherapy were any less frequent or severe than after RP or EBRT, but long-term complications are unknown.		

HTA reports/systematic reviews			
Author & year	Databases searched & search strategy	Inclusion & quality criteria	Quality assessment of review
Nilsson, Norlen, & Widmark (2004)	Searched Medline up to Jan 2003. Search terms: radiotherapy, radiation therapy, brachytherapy, prostatic cancer, prostatic neoplasms.	Study design: NHMRC level I to level IV evidence was included in the review. Patients: Prostate cancer. Interventions: Radiation therapies. Comparators: Not prespecified. Included studies compared brachytherapy with EBRT or RP. Outcomes: Not prespecified. Included studies described survival, toxicity, QoL, sexual function. Quality criteria: Studies graded as high, moderate or low quality. Application of methods: The literature search followed the principles used by the Swedish Council of Technology Assessment in Health Care.	Were inclusion/exclusion criteria reported that addressed the review question? —Yes. Was the search adequate? —Only one database was searched. Hand searching or retrieval of information from other sources was not reported. Was the validity of the included studies assessed? —Yes, but quality assessment criteria not described. Are sufficient details about the individual included studies presented? —Yes. Studies addressing I 125 were not considered separately from other implant types, hence conclusions do not relate specifically to I 125. There were no patient eligibility criteria relating to stage, Gleason's score or pretreatment PSA. Hence, some presented studies do not fit eligibility criteria for this review. Conclusions relate to brachytherapy vs 3DCRT, even though included studies compared brachytherapy with EBRT.
	Results		
	2 RCTs and 37 non-randomised studies addressing brachytherapy were included. The authors concluded that long-term (>5 yr) treatment outcome for TRUS-guided brachytherapy appears to be similar to that of RP and 3DCRT in low risk patients (PSA <10, T0–T2a, Gleason ≤ 6). Toxicity from brachytherapy with modern techniques is acceptable.		

HTA reports/systematic reviews			
Author & year	Databases searched & search strategy	Inclusion & quality criteria	Quality assessment of review
Wilt (2003)	*Clinical Evidence* search February 2003. Additional author search in Medline and Cochrane Library to 2001 for systematic reviews and RCTs. Search strategy of Department of Veterans' Affairs Coordinating Centre for the Cochrane Review Group on Prostatic Diseases.	Study design: NHMRC level I to level III evidence was included in the review. Patients: Clinically localised prostate cancer. Interventions: RP, watchful waiting, androgen suppression, brachytherapy, cryosurgery, EBRT. Comparators: Not prespecified. Included studies compared brachytherapy with EBRT or RP. Outcomes: Survival, development of metastatic disease, disease progression, time to progression, response (symptoms and signs), QoL, adverse effects of treatment. Surrogate outcomes (PSA, Gleason) where clinical outcomes not available. Quality criteria: Not stated. Application of methods: No information regarding application of methods.	Were inclusion/exclusion criteria reported that addressed the review question? —No. Was the search adequate? —Broad search of sources but search strategy not reported. Was the validity of the included studies assessed? —Yes, but quality assessment criteria not described. Are sufficient details about the individual included studies presented? —No. Studies addressing I 125 were not considered separately from other implant types, hence conclusions do not relate specifically to I 125. There were no patient eligibility criteria relating to stage, Gleason's score or pretreatment PSA. Hence, some presented studies do not fit eligibility criteria for this review. Conclusions based largely on three systematic reviews also included in this review.
	Results		
	3 systematic reviews and 1 retrospective cohort study were included. The authors reported that results were similar for brachytherapy, RP and EBRT in low risk patients (T1 or T2, PSA ≤ 10, Gleason ≤ 6).		

HTA reports/systematic reviews			
Author & year	Databases searched & search strategy	Inclusion & quality criteria	Quality assessment of review
Robinson, Moritz, & Fung (2002)	Searched Medline and Cancerlit up to December 2001. Articles published in English, French, Dutch and German were reviewed. Search terms not stated.	Study design: Unable to determine NHMRC levels of evidence included in the review. Patients: Prostate cancer. Interventions: RP, brachytherapy, cryotherapy, EBRT. Comparators: Not prespecified. Included studies compared brachytherapy with EBRT or RP. Outcomes: Erectile function. Quality criteria: Not stated. Data extracted on study quality (see below). Application of methods: Articles included if: 1) published form 1970 onwards; 2) reported results of EBRT, RP, brachytherapy or cryotherapy (with or without neoadjuvant hormone therapy); 3) reported primary, discrete data set; 4) pretreatment erectile function status known; and 5) assessment of erectile function used patient self-report. Data extracted on experimental design, type of treatment, number of subjects and mean age, patient selection criteria, definition of normal erectile function, method of assessment of erectile function, number of men with normal erectile function before and after treatment, and duration of follow-up.	Were inclusion/exclusion criteria reported that addressed the review question? —Yes. Was the search adequate? —Search terms not reported. Was the validity of the included studies assessed? —Yes, but quality assessment criteria not described. Are sufficient details about the individual included studies presented? —No. Studies addressing I 125 were not considered separately from other implant types, hence conclusions do not relate specifically to I 125. There were no patient eligibility criteria relating to stage, Gleason's score or pretreatment PSA. Hence, some presented studies do not fit eligibility criteria for this review. Comparisons between treatments are not stratified by risk group. It is likely that patients undergoing brachytherapy are generally of lower risk than those undergoing other treatments.
	Results		
	54 studies included in review (not categorised by study type). The authors concluded that brachytherapy was the treatment with the highest probability of preserving erectile function, followed by ERBT either alone or in combination with brachytherapy, nerve-sparing RP, standard RP, and cryotherapy.		

HTA reports/systematic reviews			
Author & year	Databases searched & search strategy	Inclusion & quality criteria	Quality assessment of review
Henderson, Laing & Langley (2004)	Searched Medline from 1988 to 2003. Search terms: brachytherapy, radical prostatectomy, external beam radiotherapy, quality of life, symptoms.	Study design: NHMRC level III evidence was included in the review. Patients: Early prostate cancer. Interventions: Brachytherapy. Comparators: Other commonly utilised treatments. Included studies compared brachytherapy with RP, EBRT, and brachytherpay combined with EBRT. Outcomes: QoL. Quality criteria: Not stated. Application of methods: No information regarding application of methods.	Were inclusion/exclusion criteria reported that addressed the review question? —No. Was the search adequate? —Only one database was searched. Search terms were not extensive. Was the validity of the included studies assessed? —No. Are sufficient details about the individual included studies presented? —Yes. Studies addressing I 125 were not considered separately from other implant types, hence conclusions do not relate specifically to I 125. There were no patient eligibility criteria relating to stage, Gleason's score or pretreatment PSA. Hence, some presented studies do not fit eligibility criteria for this review. Minimal information is presented about the methodology of this review.
	Results		
	5 cross-sectional and 2 prospective longitudinal studies were included. The authors concluded that brachytherapy alone or in combination with EBRT, EBRT, and RP all offer good long-term health-related QoL. Differences exist in erective function, voiding difficulty, incontinence and bowel function, which persist for 3 to 5 years post treatment (longer term QoL is unknown). Brachytherapy offers a high probability of maintaining continence, potency and normal rectal function though both storage and voiding urinary symptoms have been reported. The addition of androgen deprivation or EBRT may increase toxicity.		

HTA reports/systematic reviews			
Author & year	Databases searched & search strategy	Inclusion & quality criteria	Quality assessment of review
Harris, Lohr, Beck (2002)	Searched Medline from 1 Jan 1994 to 15 Sept 2002. Cochrane Library were also searched; experts were contacted; and review bibliographies published since1993 were scanned. Search terms: prostate neoplasms, therapeutics, treatment, surgery, prostatectomy, radiation, brachytherapy.	Study design: NHMRC level IV evidence was included in the review question relating to brachytherapy. Level I to level IV evidence was included in the whole review. Patients: Prostate cancer. Interventions: RP, brachytherapy, EBRT, androgen deprivation, watchful waiting. Comparators: As above. Outcomes: Health outcomes, harms. Quality criteria: Methods Work Group of the USPSTF criteria. Application of methods: Articles included if: 1) RCT or large cohort with control group; 2) follow-up at least 2 yrs; 3) at least 75% of pts followed; and 4) reported health outcomes. One reviewer applied eligibility criteria; other reviewers assessed studies excluded. Articles retrieved if not excluded by both reviewers. One reviewer assessed retrieved articles and discussed with another reviewer to assess eligibility. Data extracted by a single reviewer into predesigned evidence tables.	Were inclusion/exclusion criteria reported that addressed the review question? —Yes. Was the search adequate? —Yes. Was the validity of the included studies assessed? —Yes. Are sufficient details about the individual included studies presented? —Yes. Studies addressing I 125 were not considered separately from other implant types, hence conclusions do not relate specifically to I 125. There were no patient eligibility criteria relating to stage, Gleason's score or pretreatment PSA, hence some presented studies do not fit eligibility criteria for this review.
	Results		
	2 case series describing health outcomes included in review. No RCTs were identified. 4 longitudinal and 3 cross-sectional studies addressing harms of brachytherapy were included. The authors concluded that the efficacy of brachytherapy for clinically localised prostate cancer remains unknown. There is some evidence that brachytherapy has an impact on sexual, urinary and bowel function, but insufficient evidence to determine precisely the magnitude of these harms. It is estimated that 35% will have some erectile dysfunction; 2 to 12% some urinary symptoms; and 18% some bowel dysfunction 1 yr after treatment.		

HTA reports/systematic reviews			
Author & year	Databases searched & search strategy	Inclusion & quality criteria	Quality assessment of review
Wills & Hailey (1999)	Searched Cochrane Library; Medline from 1997 to August 1999; HealthSTAR from 1992 to August 1999; CancerLit from 1997 to 1999; and EMBASE and CINAHL from 1997 to April 1999. Reference lists were scanned and studies retrieved. Information was also obtained from World Wide Web searches. Search terms: prostate neoplasms, prostate, prostate cancer, brachytherapy.	Study design: NHMRC level III to level IV evidence was included in the review. Patients: Prostate cancer. Interventions: Brachytherapy. Comparators: Not prespecified, Included studies compared brachytherapy with RP, EBRT, 3DCRT, brachytherapy + hormone therapy, brachytherapy + EBRT. Outcomes: Patient outcomes (biochemical and clinical control, survival, complications). Quality criteria: Classification developed by Jovell and Navarro-Rubio—'Good' (evidence from RCTs or meta-analyses of RCTs), 'Good to Fair' (small sample RCTs or non-randomised controlled prospective trials), 'Fair' (no randomised controlled retrospective trials, cohort studies and case-control studies), and 'Poor' (case series and other approaches). Application of methods: References screened by title, then abstract, with most relevant studies obtained. No information on inclusion/exclusion or data extraction methods.	Were inclusion/exclusion criteria reported that addressed the review question? —No. Only stated that comparative studies of patient outcomes were of interest. Was the search adequate? —Yes. Was the validity of the included studies assessed? —Yes. Are sufficient details about the individual included studies presented? —Yes. Studies addressing I 125 were not considered separately from other implant types, hence conclusions do not relate specifically to I 125. There were no patient eligibility criteria relating to stage, Gleason's score or pretreatment PSA, hence some presented studies do not fit eligibility criteria for this review.
	Results		
	23 comparative and non-comparative studies were included in the review. The authors concluded that brachytherapy appears promising in the short term, but its potential for influencing overall outcomes (particularly long-term morbidity and survival) are unknown. Alternative treatments are continuing to evolve so that the safety and efficacy of brachytherapy relative to these is uncertain and may continue to change. Hence the choice of treatment will continue to be made based on physician and patient preference rather than scientific evidence of the superiority of a particular treatment modality.		

HTA reports/systematic reviews			
Author & year	Databases searched & search strategy	Inclusion & quality criteria	Quality assessment of review
Patterson (2001)	Searched Medline from 1966 to 2001, Embase from 1980 to 2001, Cochrane Library from 2001 issue 3, DARE, NHS HTA, NHS Economic Evaluation database. Search date November 2001. Search terms were not stated.	Study design: NHMRC level III evidence was included in the review. Patients: Localised prostate cancer. Interventions: Brachytherapy. Comparators: RP, watchful waiting, radiotherapy, drug treatments. Outcomes: Not prespecified. Included studies addressed failure-free survival, and urinary and sexual function. Quality criteria: Not specified. Quality was addressed in a narrative discussion. Application of methods: No information presented on application of methods.	Were inclusion/exclusion criteria reported that addressed the review question? —No. Was the search adequate? —Comprehensive sources were searched, but the search strategy was not described and hence was unable to be assessed. Was the validity of the included studies assessed? —Yes. Are sufficient details about the individual included studies presented? —Studies discussed, but no data extraction tables presented. Studies addressing I 125 were not considered separately from other implant types, hence conclusions do not relate specifically to I 125. There were no patient eligibility criteria relating to stage, Gleason's score or pretreatment PSA, hence some presented studies do not fit eligibility criteria for this review.
	Results		
	1 systematic review, 1 retrospective cohort study (2 papers), and 1 prospective cohort study were included in the review. The authors concluded that valid comparisons between brachytherapy and watchful waiting, RP, EBRT, and anti-androgen drug regimens are not possible based on the evidence identified. Until RCTs are conducted the effects of brachytherapy on mortality, urinary and sexual functioning, radiation damage to adjacent structures, and progression-free survival remain uncertain.		

HTA reports/systematic reviews			
Author & year	Databases searched & search strategy	Inclusion & quality criteria	Quality assessment of review
CETS (2000)	Searched Medline. Reference lists were also scanned. Search terms were not described.	Study design: NHMRC level III to level IV evidence was included in the review. Patients: Prostate cancer. Interventions: Brachytherapy. Comparators: Not specifically stated. Introduction states 'direct comparisons with surgery or radiotherppay would be particularly valuable'. Included studies compared brachytherapy with RP and EBRT. Outcomes: Intended and adverse effects; cost. Quality criteria: Studies graded based on design and presence of pre- and post-treatment PSA information. Narrative discussion of quality. Application of methods: No information presented on application of methods.	Were inclusion/exclusion criteria reported that addressed the review question? —No. Was the search adequate? —Only one database was searched (supplemented by reference list scanning). No search strategy was described. Was the validity of the included studies assessed? —Yes. Are sufficient details about the individual included studies presented? —Yes. Studies addressing I 125 were not considered separately from other implant types, hence conclusions do not relate specifically to I 125. There were no patient eligibility criteria relating to stage, Gleason's score or pretreatment PSA, hence some presented studies do not fit eligibility criteria for this review.
	Results		
	3 comparative studies with pre- and post-treatement PSA , 17 case-series with pre- and post-treatement PSA, and 13 case series without PSA information were included in the review. The authors concluded that it is not possible to demonstrate an efficacy advantage of brachytherapy over other treatments. It is also not possible to exclude the possibility that brachytherapy is less efficacious. Reported adverse side-effects (particularly impotence) are less frequent with brachytherapy than with RP or EBRT.		

HTA reports/systematic reviews			
Author & year	Databases searched & search strategy	Inclusion & quality criteria	Quality assessment of review
Quaranta, Marks and Anscher (2004)	Searched Pubmed. Search terms and date of search not reported. Updates published in abstract form were used when available. Search strategy to identify abstracts not reported.	Study design: NHMRC level III to level IV evidence was included in the review. Patients: Localised prostate cancer. Interventions: TRUS-guided interstitial low-dose rate brachytherapy. Comparators: RP. Outcomes: bDFS. Quality criteria: Not specified. Quality was addressed in a narrative discussion. Application of methods: Studies included if reported PSA-based outcomes, at least 100 total patients, reported standard pretreatment prognostic factors (stage, Gleason score, PSA), and had median follow-up of at least 3 yrs. No information presented on methods methods for assessing eligibility. Weighted average bNED calculated from brachytherapy series. Results from RP series were not combined.	Were inclusion/exclusion criteria reported that addressed the review question? —Yes. Was the search adequate? —Only one database was searched. No search strategy was described. Was the validity of the included studies assessed? —Not formally, but discussed in text. Are sufficient details about the individual included studies presented? —Yes. Studies addressing I 125 were not considered separately from other implant types, hence conclusions do not relate specifically to I 125. Studies addressing the low risk group (T1-T2a, Gleason score ≤6, PSA≤10) relevant to this review.
	Results		
	13 brachytherapy series (3 including brachytherapy plus EBRT) and 10 RP series addressing low risk patients were included in the review. The weighted average five-year bNED for brachytherapy in low-risk patients was 87.4%. The range for five-year bNED reported in RP series with low-risk patients was 68 to 100%. The authors concluded that excellent results were reported with both modalities, and that there is no evidence supporting the superiority of RP over brachytherapy.		

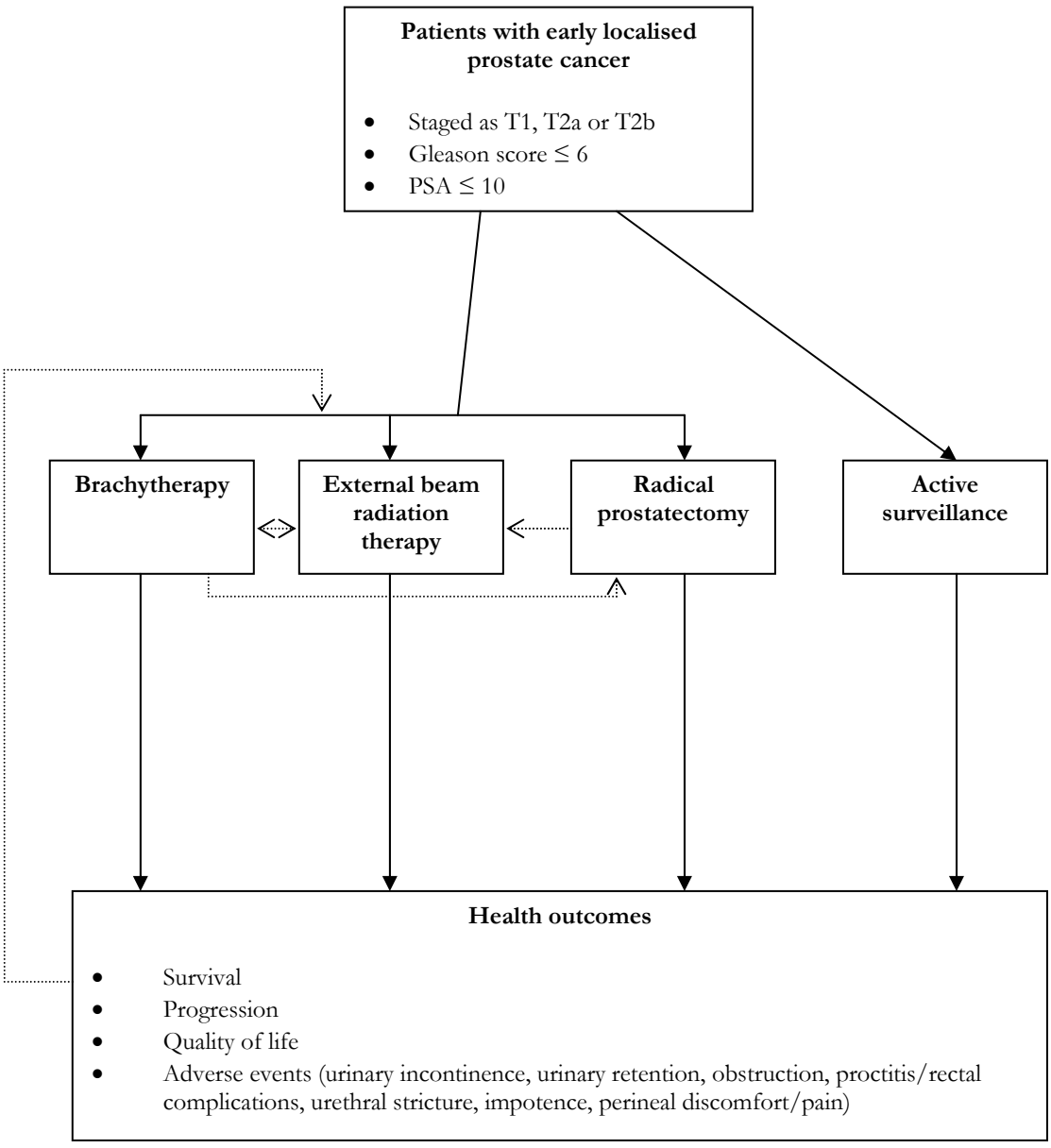
Controlled trials						
Level	Author & year	Study design	*N*	Participant characteristics	Outcomes	Quality
III-2	Stokes (2000)	Retrospective, non-randomised cohort. I 125 minimum radiation dose = 160 Gy. EBRT final target dose = 6500–7000 cGy.	*N* = 147 *n* (Brachy) = 72 *n* (EBRT) = 21 *n* (RP) = 54	Patients stratified according to risk (low, intermediate, high). Only low risk patients (T1c or T2a, Gleason ≤ 6, PSA ≤ 10) meet eligibility criteria for inclusion in review. No androgen deprivation in brachytherapy or EBRT pts.	5-yr bDFS —Brachytherapy = 78% —EBRT = 85% —RP = 78% —Data for brachytherapy and RP extracted from survival curves.	Actuarial bDFS curves presented for brachytherapy and EBRT in pts of low to intermediate risk combined. This result is not included as intermediate risk pts had PSA = 10–20, and such pts comprised 49.5% of this combined group.

Controlled trials						
Level	Author & year	Study design	*N*	Participant characteristics	Outcomes	Quality
III-2	Borchers, Kirschner-Hermanns, Brehmer et al (2004)	Prospective, consecutive, non-randomised cohort. Brachytherapy radiation dose = 145 Gy. HRQoL completed before therapy, and at 6, 12 and 24 mo. Includes EORTC-QLQ-C30 with prostate cancer module, ICS 'male' questionnaire for urinary incontinence, and Kelley questionnaire for fecal incontinence. PSA relapse defined as PSA >0.1ng/mL for RP groups, and 3 consecutive PSA rises in brachytherapy group.	*N* = 132 *n* (Brachy) = 52 *n* (RP) = 42 *n* (nerve-sparing RP) = 38	Patients staged T1–T2a/N0M0. Gleason ≤ 6. PSA ≤ 10. Prostate vol < 60 mL. Clinical and histopathological data similar in all treatment groups, except RP+NS group significantly younger. T1c = 64 (48.5%) T2a = 78 (51.5%) G2-4 = 53 (40.2%) G5-6 = 79 (59.8%) No neoadjuvant therapy.	PSA relapse-free survival: —Brachytherapy = 85% (95% CI 74–95) —RP = 96% (95% CI 91–100) —This difference is significant (p = 0.04) —Mean follow-up 27 months Survival: —Brachytherapy = 1 death at 6 mo from MI —RP = no deaths Acute morbidity: —Low, with a different profile between groups QoL: —No statistically significant differences between overall QoL. Significantly greater decrease in sexual function was observed after RP than after brachytherapy at 1 yr (p = 0.0015). —Urinary urgency higher in brachytherapy group (85%) than RP group (71%) at 1 yr (significance not reported). —Newly developed fecal soiling higher in brachytherapy group (11%) than RP (4%) and nerve-sparing RP (5%) (significance not reported).	Inclusion criteria specify prostate volume of <60mL. Proportion of pts followed up and exclusions not reported. Histopathological results of RP patients showed that 18% had extraprostatic tumours (stage ≥T3), and 63% had bilateral tumours (stage T2b [1997] or T2c [2002]). Additionally, 28% had a Gleason score upgraded to 7. Mean PSA relapse follow-up 27 mos (minimum 12 mos), where relapse can occur ≥5 yrs.

Controlled trials						
Level	Author & year	Study design	*N*	Participant characteristics	Outcomes	Quality
III-2	Ciezki, Klein, Angermeier et al (2004)	Retrospective, non-randomised cohort. Median follow-up 48 mo (range 24–94 mo). Brachytherapy radiation dose = 144 Gy. EBRT median radiation dose = 78 Gy (range 66.6–83.0 Gy).	*N* = 1074 *n* (Brachy) = 295 *n* (EBRT) = 282 *n* (RP) = 497	Only low risk patients eligible for inclusion in review. Median age = 65 (40–87) Median PSA = 6.0 (0.1–10.0) G (<6) = 146 (13.6%) G (6) = 928 (86.4%) AD therapy = 155 (14.4%) T1 = 762 (70.9%) T2a = 258 (24.0%) T2b = 38 (3.5%0 T2c = 16 (1.5%) 22.0% of Brachytherapy pts had androgen deprivation; 15.2% of EBRT pts had androgen deprivation; 9.5% of RP pts had androgen deprivation.	5 yr bRFS —Brachytherapy = 90% —EBRT = 90% —RP = 89% — (*p* = 0.82)	Implant type not mentioned in article text. I 125 determined from paper keywords. Inclusion criteria not described. Baseline comparability of treatment groups unknown.

Controlled trials						
Level	Author & year	Study design	*N*	Participant characteristics	Outcomes	Quality
III-2	Zelefsky, Wallner, Ling et al (1999)	Retrospective, non-randomised case control. Prescribed minimum I 125 radiation dose to prostate = 140–160Gy. Prescribed 3DCRT dose of 64.8 Gy (*n* = 21), 70.2 Gy (*n* = 54), 75.6 Gy (*n* = 59), and 81.0 Gy (*n* = 3).	*N* = 282 *n* (Brachy) = 145 *n* (3DCRT) = 137	Only low risk patients eligible for inclusion in review (patients staged ≤T2b; Gleason ≤ 6; PSA ≤ 10). Baseline patient characteristics similar except for significantly lower percentage of T1c pts in 3DCRT group (43%) than brachytherapy group (68%) (p<0.01), and lower percentage of pts potent in 3DCRT group (77%) than brachytherapy group (88%) (p<0.01). Median age = 68 (3DCRT), 64 (brachytherapy) Median PSA = 6.6 (3DCRT), 6.1 (brachytherapy) Neoadjuvant AD therapy = 39 (13.8%) Prior TURP = 30 (10.6%) T1c = 156 (55.3%) T2a = 61 (21.6%) T2b = 65 (23.1%)	5-yr actuarial PSA relapse-free survival: —Brachytherapy = 82% —3DCRT = 88% — (p=0.09). 5-yr actuarial likelihood of late grade 3 urinary toxicity (urethral stricture): —Brachytherapy = 12% —3DCRT = 2% — (p=0.05). —Mode of therapy the only predictor of grade 2 or higher urinary toxicity (brachytherapy > 3DCRT, p<0.0001; Cox regression). 5-yr actuarial likelihood of late grade 2 GI toxicity: —Brachytherapy = 11% —3DCRT = 6% — (p=0.71). 5-yr actuarial likelihood of erectile dysfunction among patients initially potent: —Brachytherapy = 53% —3DCRT = 43% — (p=0.52). —Higher radiation dose (3DCRT > 75.6 Gy; brachytherapy ≥ 160 Gy) the only predictor for impotence (p=0.008; Cox regression).	All pts had I 125. All pts met inclusion criteria for this review in terms of pretreatment stage, Gleason, and PSA.

Appendix D Defining the Clinical Question



Appendix E Estimated costs of brachytherapy treatment—translated from the United Kingdom and direct Australian estimates

	Sessions	Annual staff cost per 50 patients (£)	Annual staff cost per 50 patients (A$)	Staff cost per patient (A$)
Consultant radiologist	2	£11,610	$25,280	$506
Clinical oncologist	1	£5,805	$12,640	$253
Medical physicist*	2	£8,495	$18,497	$370
Consultant anaesthetist	1	£5,805	$12,640	$253
Program coordinator	0.5	£11,000	$23,952	$479
Total		£42,715	$93,008	$1,860
Total equipment costs (depreciated over 5 years) including:		£70033	$152491	
TRUS Machine				
Silicone sheath stand-off for ultrasound				
Fixation and control system for probe				
Dosimetry planning system				
Total capital cost				
Equipment cost per patient (50 patients per year 5 years)		£280.132	$610	
Miscellaneous cost items		Inpatient GBP	Inpatient AUD	
Outpatient ultrasound scan		£174	$379	
Theatre costs		£112	$244	
Overnight stay in hospital		£162	$353	
CT scan		£174	$379	
Iodine seeds***		£3500	$7621	
Needles***		£300	$653	
Total		£4422	$9629	
Total Brachytherapy costs per patient		£5,556	$12,099	
Total Brachytherapy costs including costs of adverse event treatment for moderately differentiated tumour		£8,077	$17,587	

	Australia	United Kingdom	PPP Rate
Purchase Power Parity	1.35	0.62	2.177419355

From Hummel, Paisley, Morgan et al (2003)

Abbreviations

3DCRT	three dimensional conformal radiotherapy
AIHW	Australian Institute of Health and Welfare
AJCC	American Joint Committee on Cancer
bDFS	biochemical disease-free survival
bNED	biological no evidence of disease
CETS	Conseil d'Evaluation des Technologies de la Sante du Quebec
CT	computed tomography
CTC	Clinical Trials Centre
DALY	disability adjusted life year
DARE	Database of Abstracts of Reviews of Effectiveness
EBRT	external beam radiotherapy
GI	gastrointestinal
HDR	high dose rate
HIC	Health Insurance Commission
HR	hazard ratio
HRQoL	health related quality of life
HTA	health technology assessment
ICD	International Classification of Diseases
I 125	iodine 125
MBq	megabequerel
MBS	Medicare Benefits Scheme
MSAC	Medical Services Advisory Committee
NHMRC	National Health and Medical Research Council
PLYL	person life years lost
PSA	prostate specific antigen
QALY	quality adjusted life year

QoL	quality of life
RCT	randomised controlled trial
RP	radical prostatectomy
SEER	surveillance epidemiology and end results
TG-43	American Association of Physicists in Medicine Task Group 43
TGA	Therapeutic Goods Administration
TNM	tumour–nodes–metastasis
TRUS	transrectal ultrasound
TURP	transurethral resection of the prostate
UK	United Kingdom
YLD	years lost due to disability
YLL	years of life lost

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