Brachytherapy for the treatment of prostate cancer

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MSAC application no. 1029

Assessment report

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The Medicare Services Advisory Committee is an independent committee which has been established to provide advice to the Commonwealth Minister for Health and Aged Care 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.

This report was prepared by the Medicare Services Advisory Committee (MSAC) with the assistance of Dr Jenny Doust of the Australasian Cochrane Centre. The report was endorsed by the Commonwealth Minister for Health and Aged Care on 9 February 2001.

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

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Brachytherapy is the treatment of localised prostate cancer by implanting radioactive seeds into the prostate gland. This review has assessed the effectiveness and safety of brachytherapy for localised prostate cancer. The application to MSAC for this procedure has specified patients who are clinical stage T1, T2a or early T2b, Gleason 2-6 and PSA < or = 10 ng/ml.

Medicare Services Advisory Committee - role and approach

The Medicare Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Aged Care 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 the available evidence is thus the basis of decision making when funding is sought under Medicare. A team from the Australasian Cochrane Centre was engaged to conduct a systematic review of literature on brachytherapy for early prostate cancer. A supporting committee with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of brachytherapy in early prostate cancer

Clinical need

Prostate cancer is the second most common cause of cancer death of Australian males. About 14,000 men are diagnosed with prostate cancer annually and of these 2,500 will die from it. The main management options for localised prostate cancer are radical prostatectomy, external beam radiotherapy, brachytherapy and watchful waiting. Data indicated that, in Australia, about 7000 men are diagnosed with clinically localised prostate cancer each year and of these about 4,000 will undergo specific therapy.

Safety

While side effects are possible for all treatment options for localised prostate cancer, brachytherapy may be less likely to result in impotence or urinary incontinence. Side effects of brachytherapy may be experienced during or shortly after treatment or over a longer timeframe. Possible short-term side effects of brachytherapy include irritation of the bowel or bladder. Side effects that may occur later, in a small number of cases, include urethral narrowing, injury to the rectum and impotence.

Effectiveness

There is limited information on the relative effectiveness of brachytherapy treatment. It can be considered as a first line treatment for patients who are fully informed of the potential risks and benefits of each of the alternative treatments available. The ideal patient for brachytherapy is a patient with low volume, low grade to intermediate grade disease with greater than a 10-year life expectancy. It is contraindicated in patients with high grade tumours and in those who have previously had a transurethral resection of the prostate.

Cost effectiveness

A full economic evaluation of treatment options including the costs of treating complications has not been undertaken. The estimated relative costs of brachytherapy, radical prostatectomy and radiotherapy in this report are based on information provided by the applicant and members of the supporting committee.

If approximately 20 per cent of patients with localised prostate cancer each year (800 patients a year in Australia) were to choose to have brachytherapy, the annual cost would be approximately $9,500,000. The additional cost compared with prostatectomy is approximately $3,500 per patient, or $2,800,000 per annum.

It would appear that the direct costs of brachytherapy for the treatment of localised prostate cancer are slightly higher than those of other treatments. However, these costs need to be weighed against possible indirect savings. Some complications are possibly less common with brachytherapy, particularly the risk of sphincteric incontinence and impotence. Patients also require substantially less time in hospital, and off-work when treated with brachytherapy than with either EBRT or prostactetomy.

Recommendation

MSAC recommends that from the evidence pertaining to brachytherapy for the treatment of prostate cancer (MSAC Application no. 1029), interim public funding should be supported for patients with prostate cancer:

- at clinical stages T1, T2a or T2b, with Gleason Scores of less than or equal to 6, prostate specific antigen (PSA) of less than or equal to 10 ng/ml, a gland volume less than 40 cc and with a life expectancy of more than 10 years; and
- where the treatment is conducted at approved sites.

This recommendation is to be reviewed no later than three years from the date of this report.

The Minister for Health and Aged Care accepted this recommendation on 9 February 2001.

Introduction

The Medicare Services Advisory Committee (MSAC) has reviewed the use of brachytherapy, which is a form of radiotherapy used in the management of localised cancer of the prostate. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme for 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 in localised prostate cancer.

Background

Brachytherapy

The procedure

Brachytherapy is the implantation of radioactive seeds directly into the prostate gland. Under ultrasound guidance (using a transrectal ultrasound probe), radioisotopes are inserted into the prostate gland. Implantation may be carried out as a one-off, day-patient procedure. The radioactive seeds have a localised effect by destroying 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 (^{125}I) seeds and temporary implants using Ir-192 via temporary catheters. Permanent implants only are the subject of this application.

Since 1984, radioactive seeds have generally been implanted via the perineal percutaneous route. Before 1984, seeds were generally placed in a retropubic, free-handed manner, often with pelvic lymph node dissection. The retropubic approach gave a higher complication rate and is no longer used. Data using this approach have not been considered as part of this review.

The form of radioisotope in use in Australia is ^{125}I. Palladium (^{103}Pd) implants are not currently available in Australia, although studies of this technique have not been excluded in the preparation of this report. Each ^{125}I implant seed usually has an activity of 0.3-0.4 mCi, with the dosage occurring within the range of 0.18–0.70 mCi, and with a six per cent spread. The total radiation dose is about three times that from external beam radiotherapy, but implantation allows the radiation field to be concentrated more directly in the target area. Implantation may be used with prior adjuvant hormonal therapy to decrease the tumour volume. It is also sometimes combined with external beam radiotherapy as 'combination therapy'. The procedure requires the combined services of a urological surgeon and a radiation oncologist.

Intended purpose

Brachytherapy is a therapeutic option for managing localised prostate cancer, that is prostate cancer staged as T1 or T2. Prostate cancer is staged using a TNM staging system (see Table 1). It is also graded using a histopathological classification system known as the Gleason score (see Table 2).

Table 1 Classification of stage of prostate cancer (TNM) (1997 criteria)

Classification		Feature described
T Classification		**Tumour type**
T1		*Clinically inapparent tumour which is neither palpable nor visible by imaging*
	T1a	Incidental histologic finding in 5% or less of prostate tissue resected
	T1b	Incidental histologic finding in greater than 5% of prostate tissue resected
	T1c	Identified by needle biopsy (eg because of elevated PSA levels)
T2		*Tumour is confined within the prostate*
	T2a	Tumour involves 1 lobe
	T2b	Tumour involves both lobes
T3		*Invasion outside of the prostate*
T4		*Distant metastasis*
N Classification		**Extent of lymph gland involvement**
Nx		Presence or absence of cancer in the pelvic lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1-N3		Increasing extent of lymph node involvement
M Classification		**Extent of metastasis**
Mx		Presence or absence of distant metastasis cannot be assessed
M0		No distant metastasis
M1a-M1c		Increasing extent of metastasis to other sites in the body

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

Gleason grade	Histopathology
G 0-4	Well differentiated
G 5-7	Moderately differentiated
G 8-10	Poorly differentiated or undifferentiated (marked anaplasia)

Assessing data for prostate cancer treatment is complicated by the marked changes that have occurred in pre- and post-intervention monitoring. The staging has changed in recent years from the AUC system to the TNM system. The UICC TNM system of 1987 was changed in 1997 (UICC 1997), reducing the subdivision of the T2 category from T2a, T2b and T2c to that in the above table. This makes it awkward to compare the reports of outcomes of treatment by stage from different time periods (see results section below), although the vast majority of publications report pre-1997 patient series because of the length of follow-up time.

The application for approval of ^{125}I brachytherapy has indicated the intention that brachytherapy be used to treat only early, localised prostate cancer, that is, patients in clinical stage T1, T2a or early T2b with a Gleason score of 2–6 and a PSA <10.

Contraindications

Brachytherapy is contraindicated in patients:

- with a previous history of a transurethral resection of the prostate (TURP);
- 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 cc because of difficulties with seed implantation - however, patients with a prostate gland greater than 40 but less than 60 cc may be treated with 3-6 months of androgen blockade to decrease the prostate size, making the prostate gland more suitable for brachytherapy.

It is generally considered 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 be in this group. Patients who have a Gleason grade of 7 or more or a PSA or greater than 10 have a high probability of extracapsular disease and are not normally treated by brachytherapy alone. Such patients have been treated by a combined brachytherapy and external beam radiotherapy but data on the effectiveness and safety of this treatment are extremely limited (see results section below).

Clinical need / burden of disease

Epidemiology of prostate cancer

Trends in incidence and mortality

Prostate cancer is the second leading cause of cancer death in males in Australia (Australian Bureau of Statistics, 1996). The incidence of prostate cancer rose steadily before peaking in Australia during the 1990s (likely to be a reflection of trends in uptake of informal PSA screening), but now appears to be declining (Australian Health Technology Advisory Council, 1996; South Australian Cancer Registry, 1998). The incidence would be expected to increase as a result of the aging of the population, even were age-specific incidence rates to remain stable. In addition, the increased use of methods to detect prostate cancer, such as the prostate specific antigen test (PSA), has resulted in an increase in the detection of the disease, which is reflected in the incidence data.

Australian data

The lifetime risk of developing prostate cancer (to age 74 years) for a man born in Australia has recently been calculated as close to 13 per cent, with mortality from prostate cancer in this age group estimated to be 1.5 per cent (Coates and Armstrong, 1997). Jelfs et al. (1996) reported that, in Australia in 1995, 14,000 new cases of prostate cancer were identified and that 2,500 deaths were caused by it. About 7000 of these identified cases will have localised disease, that is, disease that has not yet spread outside of the prostate gland. Prostate cancer occurs most in males aged 65-75 years (the disease being relatively rare in younger age groups), but 30 per cent of all new cases for 1995 were in men older than 75 years (Jelfs et al. 1996). The data in Table 3 are unadjusted for age, but age-adjustment also confirms the recent downward trend.

Table 3 Incident cases, SA Cancer Registry

Year	Number of cases
1989	480
1993	1107
1994	1301
1995	1240
1996	972
1997	1059

Mortality from prostate cancer has been stable in Australia in the past decade, although 1997 data from the South Australian Cancer Registry (1998) show a non-significant decrease.

US data

The surveillance, epidemiology and end results (SEER) program provides population-based cancer data from nine registries at various locations in the United States. The combined SEER data are taken from approximately 14 per cent of the US population, and are often considered the best approximations of cancer trends for the US population as a whole.

In a recent population-based study, Prorok et al. (1996) used Medicare claims data (pertaining to procedures used to detect and diagnose prostate cancer) and SEER data to investigate rising prostate cancer incidence. A random sample of Medicare beneficiaries aged 65 years and older without cancer and men with prostate cancer diagnosed at 65 years of age and older was examined. The authors found that age-adjusted incidence of prostate cancer rose by 82 per cent during the period 1986 to 1991, with the highest rates of increase in 1990 (20%) and 1991 (19%). During the same period, the data indicated that the number of prostate needle biopsies and PSA tests performed each year increased, while the number of transurethral resections of the prostate (TURP) declined. The authors concluded that the rises in prostate cancer incidence were most likely a result of changes in screening practices.

Trends in the SEER data have been the subject of considerable analysis in the literature. It is widely agreed that while the peak in prostate cancer incidence was primarily caused by PSA-based screening, there was a modest increase before the PSA era, which it is thought may reflect changes in the prevalence of risk factors in the population.

Trends in survival

Survival rates, a measure of the proportion of patients still living at specified times following diagnosis, provide an important measure of the impact of prostate cancer. The most recent SEER report (National Cancer Institute, 1998) provides a detailed analysis of trends in survival in the US population. A five-year survival rate of nearly 70 per cent was found in men diagnosed in 1990, and this represents a 50 per cent increase on rates observed for men in 1973. Survival rates adjusted for other causes of death have also improved consistently for localised and regional stage cancer and for all cancer grades, but five-year survival for distant disease did not improve during the period studied. Survival rates for men aged less than 50 years are less than those for men diagnosed at older ages.

Natural history of prostate cancer

Several studies have demonstrated the heterogeneous nature of prostate cancer. Histologic evidence of prostate cancer can be found in 30-40 per cent of men aged above 50 years, but only one in four of these cancers will become clinically evident and only one in 14 will be the cause of death (Abbas & Scardino, 1997). One of the current difficulties in diagnosing prostate cancer at an early stage is that it is not possible to differentiate clinically significant tumours from those that present no threat to life. While histological, molecular, morphological and other markers exist, none of these are currently able to predict disease progression accurately.

Staging and grading of prostate cancer

The ability to stage and grade prostate cancer accurately is of vital importance in determining prognosis, and forms the basis for initial management decisions. Strategies for determining the stage and grade of a tumour are:

- histopathological grading of biopsy or surgical specimens;
- diagnostic imaging (CT scan, MRI and radionuclide bone scans); and
- surgical staging by examination of regional lymph nodes.

It has also been demonstrated that pre-treatment PSA is predictive of metastatic disease and may be a more important indicator than tumour staging and grading. Cancer patients with baseline PSA levels higher than 15 ng/mL but with only stage T1-T2 cancer may have outcomes as poor as patients with T3-T4 disease and even worse than T3-T4 patients with lower baseline PSA levels (Zietman, 1994b).

Prostate volume and pre-treatment PSA are also effective predictors of freedom from recurrence after radical prostatectomy (D'Amico et al. 1997).

Existing procedures

The management of localised prostate cancer continues to be an uncertain and contentious area of medicine. There have been few studies that adequately compare the various treatment options. Rapid developments in the area also mean that long-term data on current treatment methods are not available.

The various options for managing localised prostate cancer are summarised below. For a more complete discussion of these therapies, see the NHMRC report *'The Management of Localised Prostate Cancer'*.

Comparators

Radical prostatectomy

Radical prostatectomy is the complete, surgical removal of the prostate gland. Radical prostatectomy is a major operation, with an average operating time of 2-4 hours, an average stay in hospital of 3-6 days (American Urological Association, 1995) and a convalescent period of about four weeks.

There are two surgical approaches - perineal or retropubic. In the perineal one a separate incision is made for lymph node dissection, although laparoscopic lymphadenectomy can also be used with this technique.

The complication rates for radical prostatectomy are highly variable and difficult to predict (eg see Fowler et al. 1995; Murphy et al. 1994; Wasson et al. 1993). Urinary incontinence and impotence, however, are two of the most commonly reported complications, and both clearly reduce quality of life. Due to non-standardised definitions and differing survey techniques, reports on severity and frequency of disability vary considerably.

In 1983, Walsh and his associates published results of their nerve-sparing technique for radical prostatectomy. This technique aims to spare one or both of the neurovascular bundles that carry the nerves needed for potency and normal functioning of the urinary sphincter. It appears to have fewer complications and results in reduced rates of urinary incontinence (Kaye et al. 1997).

External beam radiation therapy

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. Conformal therapy is a way to increase the radiation dose of EBRT by targeting the diseased tissue more accurately.

Acute complications include rectal bleeding, cystitis, diarrhoea, proctitis, haematuria and skin reactions. Urethral stricture, impotence, rectal and bladder ulceration and chronic cystitis are among the most common longer term complications described (Selley et al. 1997). Three to five per cent of patients suffer severe rectal damage. Again, studies report considerable variation in the frequency, type and duration of complications (Helgason et al. 1996; Mantz et al. 1997; Shrader-Bogen et al. 1997).

It is difficult to compare studies of external beam radiotherapy 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 is either not stratified by stage or is not comparable to that for patients who have undergone surgery.

No initial treatment or deferred treatment

As discussed above, a proportion of patients who are diagnosed with prostate cancer do not progress to life-threatening disease. An approach sometimes termed 'watchful waiting', may be used. This strategy delays treatment until the patient becomes symptomatic or develops complications from their prostate cancer. 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 watchful waiting is chosen. However by deferring treatment, the patient avoids any potential complications from the more active forms of treatment.

There is some data suggesting 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 - particularly as patients selected for watchful waiting are frequently those with low grade disease. Studies to date have all been case series or analyses of population cancer registry data (Chodak, 1994, Albertsen, 1998, Adolfsson et al. 1997, Johanssen et al. 1997, Borre et al. 1997, Brasso et al. 1998, Lu-Yao and Yao, 1997) and therefore provide only a low level of evidence. Deferred treatment may be an option for elderly patients who may have short life expectancies.

A comparison between brachytherapy and deferred treatment 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 external beam radiotherapy and conformal radiotherapy. The safety and effectiveness of this are not yet adequately established.

Marketing status of the device / technology

Listed with the Therapeutic Goods Administration (AUST L67687 and AUST L58303).

Current reimbursement arrangement

There is no current Medicare Benefits Schedule reimbursement arrangement for brachytherapy for prostate cancer.

Approach to assessment

This review of the evidence of literature on the effectiveness and safety of brachytherapy has followed the methods outlined in the *'Cochrane Collaboration Handbook'* as closely as possible (Mulrow and Oxman (eds), updated 1997).

Review of literature

The medical literature was searched to identify relevant studies and reviews published between 1990 and March 2000. Searches were done of the MEDLINE, EMBASE and CANCERLIT databases.

The search terms used were 'prostate cancer', 'brachytherapy', 'iodine implant/ation', 'prostate implant/ation', 'prostatectomy' and 'radiotherapy'. Only articles published since 1990 were considered because the current form of brachytherapy used in Australia was developed after 1990 and it was considered that earlier literature was irrelevant.

Table 4 outlines the designation of levels of evidence as outlined by the NH&MRC Guidelines. For therapeutic interventions, the highest quality of evidence is that from properly conducted, randomised controlled trials or from a systematic review of randomised controlled trials. For treatment of localised prostate cancer there are no such studies available.

Table 4 Designation of levels of evidence

I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly designed, randomised, controlled trial.
III-1	Evidence obtained from well-designed, pseudo-randomised, controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies or interrupted time series with control group.
III-3	Evidence obtained from comparative studies with historical control, two and 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 and post-test.

Source: NHMRC 1999.

Expert advice

A supporting committee with relevant expertise was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for supporting committees, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the supporting committee is provided in Appendix B.

Results of assessment

Is it safe?

Studies examining complication rates of brachytherapy

The primary advantages of brachytherapy over radical prostatectomy and external beam radiotherapy are its potential for potency preservation, its relatively short treatment time and its avoidance of surgical risks. Potential complications at the time of treatment are haematuria (which is generally mild and self limiting), dysuria, urinary obstructive symptoms and gastrointestinal complications, such as proctitis. Obstructive problems may require catheterisation.

Late complications of brachytherapy included urethral stricture, rectal irritation and impotence. It appears, however, that potency is more likely to be preserved after brachytherapy than after other forms of therapy for localised prostate cancer, especially radical prostatectomy. Incontinence has also been recorded as a complication in several studies, but mainly in patients who have had a TURP before radiotherapy. There is also a potential risk of seed embolisation to the lung with free seed implants. However, this has not been demonstrated to cause clinical morbidity. The small amount of data available from patients treated in Australia is in line with the complication rates reported in this review.

Complication rates appear to have fallen in more recent case series, probably because of increased experience with the technique. The risk of complications (D'Amico et al. 1996) is lower in patients:

- with no history of a prior TURP;
- with a prostatic volume of less than 60 cc;
- who receive a lower dose; and
- for whom central loading is avoided.

Studies reporting complication rates of brachytherapy are shown in Table 5 and details of the complication rates in Table 6. The study by Zelefsky et al. (1999) compares results of patients treated at the Memorial Sloan Kettering Cancer Centre between 1988 and 1995. Subjects had PSA scores lower than or equal to 10 ng/ml, a Gleason score of 6 or less and a cancer of stage less than or equal to T2b.

The selection of a mode of therapy for patients was determined by their preference, with all being offered a choice of all the treatments. Due to the lack of randomisation, it is difficult to attribute any difference in outcomes to the type of procedure used, but in this group of patients brachytherapy resulted in more cases of severe urinary retention, urethral stricture and impotence than in other case-series reports.

Table 7 attempts to summarise the complication rates for each of the main types of therapy used in the management of localised prostate cancer. Further details of the studies examining radical prostatectomy and external beam radiotherapy are included in the NH&MRC report. This report is presently being revised. It should be noted that the incidence of complications has also fallen over time with the improvement in other techniques. This is particularly true for prostatectomy for which the introduction of nerve-sparing techniques has reduced the incidences of incontinence and impotence. The comparisons in this table should be interpreted with great caution because of the major differences in patient populations and in the ways in which outcomes have been recorded in different studies.

It has been demonstrated that the safety and effectiveness of brachytherapy are related to the planning of dosage and placement of radioactive seeds. This requires a multi-disciplinary team with appropriate skill and experience in performing the procedure.

Table 5 Studies reporting complications post-brachytherapy

Reference	Setting	No of pts	Grade/stage	Method	Average age at diagnosis	Months followed
Benoit et al. (2000)	Medicare patients in USA	2124	Not reported	All patients in USA who had brachy-therapy in 1991	Not reported	Until end of 1993
Grado (1998)	Mayo Clinic, Scottsdale, Arizona	Total n = 490 Brachytherapy = 418 alone Brachytherapy = 72 with EBRT	T1 = 5% T2a = 32% T2b = 50% T3 = 6% >T3 = 7%	Ultrasound-guided percutaneous ^{125}I or ^{103}Pd implantation (with and without prior androgen deprivation) alone or with EBRT	Not reported	Median = 46.9 (range 22-95)
Kaye et al. (1995)	Minnesota	76	T1b = 7% T2 = 93% PSA > 4 = 79%	Percutaneous ^{125}I implantation (with and without EBRT)	71 (50-83)	26.3 (range 11-60)
Koutrouvelis (1998)	Vienna, Virginia	130	Localised stage A, B or C	3-dimensional stereotactic CT-guided ^{125}I and ^{103}Pd implantation (with and without prior and/or subsequent hormone manipulation)	Median = 71 (range 49-90)	Ranged from 6-24
Ragde et al. (1997)	Seattle, Washington	122	T1a = 4% T1b = 3% T1c = 16% T2a = 62% T2b = 14% T2c = 1% PSA median = 5.0ng/mL (range 0.2-74.6 ng/mL)	TRUS-guided ^{125}I implantation	Median = 70 years	Median 69.3

Table 5 continued

Reference	Setting	No of pts	Grade/stage	Method	Average age at diagnosis	Months followed
Stone and Stock (1999)	Mount Sinai Medical Center, New York	301	'Low risk' = 36% T2a or less, Gleason 6 or less, PSA 10 ng/mL or less 'Moderate risk' = 51% T2b-T2c, Gleason 7 or more, PSA 11-15 ng/mL 'High risk' = 13% T2c-T3c, Gleason 8 or more, PSA 16 ng/mL or more	Low risk: TRUS-guided implantation of ^{125}I High risk: ^{125}I or ^{103}Pd with and without 5 months hormonal therapy High risk: Brachytherapy, EBRT and 9 months hormonal therapy	Not reported	Low risk: median = 18 (range 12-84) Moderate risk: median = 27 (range 12-74) High risk: median = 13 (range 6-42)
Wallner et al. (1994)	Memorial Sloan-Kettering Cancer Center	62	T1b = 3% T1c = 21% T2a = 40% T2b = 27% T2c = 8% PSA>4= 90%	CT planned transperineal ^{125}I implantation	67 (58-80)	19 (range 6-55)
Zelefsky et al. (1999)	Memorial Sloan-Kettering Cancer Center	Total group = 282 Brachytherapy = 145 EBRT = 137	Total Group: TT1c = 55% T2a = 22% T2b = 23% Note: larger proportion of T1c in brachy-therapy group PSA median = 6.1 (brachytherapy) and 6.6 (EBRT) ng/mL	CT planned transperineal ^{125}I implantation or: Conformal EBRT	Brachytherapy: median = 64 years EBRT: median = 68 years	Brachytherapy: median = 24 (range 6-103) EBRT: median = 36 (range 12-109)

Table 6 Complications of brachytherapy

Primary author	Urinary incontin-ence	Urinary retention	Obstruction/ irritative sex	Proctitis/ rectal complications	Urethral stricture	Impotence	Urethral necrosis	Perineal discomfort/ pain
Benoit et al. (2000)	6.6%		8.3%	5.5%		8.4%		
Grado (1998)				1%				0.8%
Kaye et al. (1995)	18%		28%	9%	3%	55%[(a)]	3%	20%
Koutrouvelis (1998)	0%			0%		5%		
Ragde et al. (1997)	5.1%				14%			
Stone and Stock(1999)	All patient groups: 0%			Low and moderate risk: grade 1-2 =4.5 and 4%, grade 3-4= 0% High risk: grade 2 = 18% (grade 3-4 prevalence not reported)				
Wallner et al. (1994)	0%		5%	12%	6%	50%[(b)]		
Zelefsky et al. (1999)		Grade 3 = 3% (brachytherapy) Grade 3 = 0% Grade 2 = 42% (EBRT)		11% (brachytherapy) 6% (EBRT)	7% (brachy-therapy) 1% (EBRT)	53%[(c)] (brachy-therapy) 43%[(d)] (EBRT)		

(a) 25% if those impotent pre-treatment are excluded

(b) 21% if those impotent pre-treatment are excluded

(c) 19% if those impotent pre-treatment are excluded

(d) 9% if those impotent pre-treatment are excluded (reported proportion refers to 5-year likelihood of dysfunction)

Note — the percentage of patients suffering from impotence and incontinence in this table is the number of men who are impotent post-operatively divided by the number treated. This has been done to remain consistent across the results of all the trials, including those where pre-operative potency and continence status is not known. The percentage includes, however, the percentage of men who were impotent or incontinent prior to treatment, and not just those who suffered these as complications of treatment.

1) Kaye et al. (1995). Potency was assessed in 72% of the patients. Of the 44 who were potent before the implant, 75% of them were still maintaining erections adequate for intercourse at 1 year.
2) Wallner et al. (1994). Of the 38 patients who were sexually potent before implantation, 81% remained potent at 3 years.

Table 7 Complication rates of brachytherapy, radical prostatectomy, external beam radiotherapy

	* Brachytherapy	†External Beam Radiotherapy	‡Prostatectomy
Death	0%	0%	0-1%
Faecal incontinence	NR	NR	2-16%
Rectal complications	0-12%	2-11%	1-20%
Obstruction/irritative urinary symptoms	5-28%	4-5%	12-20%
Urethral stricture	3-14%	5%	1-20%
Urinary incontinence	0-6.6%[(a)]	5-7%	7-59%
Impotence	5-55% 5-25%[(b)]	23%-80%	32-89%
Perineal discomfort/pain	1-20%	?	NR

* see Tables 5 and 6 for studies included in this analysis

† Studies included in this analysis: Fowler et al. (1996); Helgason et al. (1995); Helgason et al. (1997); Mantz et al. (1997); Shrader-Bogen et al. (1997); Wasson et al. (1993)

‡ Studies included in this analysis: Fowler et al.. (1995); Helgason et al. (1997); Jonler et al. (1994); Kaye et al. (1997); Murphy et al.(1994); Shraader-Bogen (1997); Walsh et al. (1994); Wasson et al. (1993); Stanford et al. 2000

NR The complication was not reported by any of the studies which are included in this table.

(a) The incidence of incontinence is very low in those patients who have not had a history of a TURP

(b) The incidence of impotence where pre-treatment impotence is excluded

Note that the ranges reported in this table are the range of point estimates reported in the literature. The true value may therefore lie outside this range.

Is it effective?

Studies examining survival and progression rates

Studies examining biochemical relapse-free survival after brachytherapy are summarised in Table 8. Further details of these studies are in Appendix C. The biochemical relapse-free survival data obtained from these studies are summarised in Table 9. For comparison, the biochemical relapse-free survival rates for patients treated with prostatectomy and external beam radiotherapy are presented in Tables 10 and 11.

One of the difficulties in interpreting the results of the various studies is a lack of agreement on the definition of failure after treatment. One of the most common measures used is that of biochemical failure, that is an indication of rising PSA levels. This is the measure presented in the following tables, but as can be seen from the tables, the way this is defined varies considerably between the studies and there is little of the consistency needed to allow a direct comparison between the studies.

Comparisons of survival data from the case series are also likely to give a biased representation of treatment effectiveness. Elderly patients or those with an intercurrent illness have been shown to be less likely to receive surgery and more likely to receive EBRT, brachytherapy or no active treatment. All-cause mortality would therefore be higher in these groups, even if the treatments were equally effective. However, because of the large proportion of patients removed from the population because of death from other causes, cause-specific mortality may not give an accurate estimate of effectiveness.

For example, the overall survival rate for patients with stage T1 or 2 disease and given no active treatment in the case series recorded by Johanssen et al. was 19.8 per cent at 15 years. However, the cause-specific mortality rate was only 19.1 per cent, giving a corrected survival rate of 80.9 per cent. The introduction of PSA screening has also resulted in lead-time and length-time bias that can result in later series appearing to have higher survival rates than earlier series. Although there are many difficulties with the interpretation of this data, an attempt has been made to summarise the available data on cause-specific mortality rates for each of the treatment options and the results are shown in Table 12. Further details of the studies included in this table are available in the NH&MRC report.

One of the largest series of patients comprises those treated at the Northwest Hospital in Seattle. The results published by Ragde et al. in 1998 and Ragde and Kolb in 2000 showed that the five- and ten-year biochemical relapse-free rates for brachytherapy were 71 and 66 per cent respectively. As suggested by the authors, the results of this study are comparable to those achieved after radical prostatectomy or external beam radiation. Nonetheless, this patient population had a relatively low median baseline Gleason score of 4 or less and more than 40 per cent had baseline PSA levels of only 0-4 ng/mL. The authors suggest that factors that may have contributed to cases of treatment failure were:

- flawed dosimetry from inaccurate volume determination based on intra-operative caliper measurements of the prostate;
- failure to obtain homogenous distribution of the nomogram-calculated dose, due to frequent erratic seed placement within the target volume associated with the freehand implantation technique;
- selection of patients with locally advanced disease not detected by clinical staging; and
- sub-optimal dose of ^{125}I (particularly in the case of rapidly growing tumours).

The study by D'Amico et al. (1998) is important as it is one of the few examples of a comparative study that were identified. It is a retrospective cohort study that has been stratified by predictive factors, such as stage, Gleason score and PSA level. This study and the study by Zelefsky et al. (1999) would be assessed as Level 3 evidence; all the other studies included in this review are Level 4.

The study by D'Amico et al. (1998) compared PSA relapse-free survival after brachytherapy, prostatectomy and EBRT for clinically localised prostate cancer. A total of 1872 patients were treated between 1989 and 1997 at multiple centres in the USA for stage T1c-T2c tumours. Of these, 218 were treated with perineal, template-guided, ^{103}Pd implantation with and without androgen deprivation (median follow-up 41 months), 888 underwent radical retropubic prostatectomy and bilateral pelvic node sampling (median follow-up 38 months), and 766 underwent conformal EBRT (median follow-up 38 months). The authors report no statistical difference in 5-year PSA outcome for any treatment (with or without androgen deprivation) for patients in the low-risk group[1].

[1] Similar to the indicated group described in the application, in this study the 'low-risk group' is defined as up to stage T2a; PSA ≤ 10 ng/mL; Gleason ≤ 4.

Patients considered at intermediate or high risk of relapse were more likely to do so if treated with brachytherapy. It should be noted that the survival rates for all treatment modalities were high for patients with low-risk prostate cancer, and that they were not compared with a group treated with watchful waiting. The survival curves for the different treatment groups stratified by risk group are shown in Figures 1-4.

Polascik et al. (1998) compared case-series data available for patients treated by radical prostatectomy at Johns Hopkins Hospital with patients treated by brachytherapy at the North West Tumor Institute in Seattle. The data showed a higher relative proportion of patients with biochemical disease-free status in the patients treated by surgery, but the baseline characteristics between the two groups differed markedly.

Critz et al. (1997) have published data on disease-free survival rates for 1020 men who were treated with a combination of brachytherapy and external beam radiotherapy. Their cancers were at the clinical stages T1 and T2. The 5-year and 10-year biochemical relapse-free rates for men treated by the ultrasound-guided, perineal brachytherapy technique were 92 and 73 per cent respectively.

As the data on biochemical disease-free survival shows high survival rates for men in all treatment groups, the question arises whether the natural history of low and intermediate grade disease is relatively benign and whether deferred treatment (sometimes called 'watchful waiting') may also be effective. Unfortunately, there is only one small study that has directly compared active treatment with deferred treatment. This showed no difference in survival between surgery and deferred treatment after 23 years, although the study was too small to detect a clinically significant difference between the two groups (Iversen et al. 1995). Some of the most important studies examining deferred treatment that have been published are as follows.

1) Albertsen et al. (1998)

Albertsen and colleagues assembled a cohort of 771 men from the Connecticut Tumour Registry who they managed conservatively (although hormone treatment was offered) before examining their survival 15-years post-diagnosis. Prostate cancer mortality was highly correlated with Gleason score:

Gleason score	Death from prostate cancer
2–4	6%
5–6	20%
7	45%
8–10	63%

Men with a high Gleason score had a significant risk of death from prostate cancer even when diagnosed up to the age of 75 years.

2) Johanssen et al. (1997)

This study now has 15-year, follow-up data. It followed a group of 642 patients with prostate cancer of any stage, consecutively diagnosed between 1977 and 1984 at a mean age of 72 years with complete follow-up to 1994. Prostate cancer accounted for 37 per cent of all deaths. Of the 300 patients with localised disease (T0-2), 11 per cent died of prostate cancer.

In the group with localised disease, the 15-year survival rate was similar in 223 patients with deferred treatment (81%, 95% CI, 72%-89%) and in 77 who received initial treatment (81%, 95% CI, 67%-95%).

The authors found an overall, long-term corrected survival rate that was slightly higher than for the whole of Sweden.

3) Lu-Yao & Yao (1997)

The 'no-intervention' arm of this population-based analysis of cancer registry data, examining overall- and prostate-cancer-specific survival in men undergoing active or conservative management is one of the largest cohorts available. Ten-year, prostate-cancer-specific survival for those in the conservative management group, by grade of cancer, was:

- low grade: 93% (95% CI 91-94)
- intermediate grade: 77% (95% CI 74-80)
- high grade: 45% (95% CI 40-51)

These results compare with cause-specific actuarial survival rates post-radical prostatectomy of: low grade - 94 per cent, intermediate grade - 87 per cent and high grade - 67 per cent.

Due to the differences between populations in prevalence of screening, it is difficult to compare these studies and treatment ones. The benefits of treating localised prostate cancer can only be determined by a randomised controlled trial. The prostate cancer intervention versus observation trial (PIVOT) is currently underway in the United States, and is expected to publish results in ten to fifteen years. The recruitment target for this trial is more than 1000 men. So far nearly 700 men have been enrolled in the trial, after approximately five years of recruitment.

Another trial which had been funded by the UK Medical Research Council had sought to investigate the differences between treatments and deferred treatment in incidentally diagnosed (not screen detected) cancers. This trial was discontinued because of recruitment difficulties in the early 1990s.

Table 8 Studies examining biochemical disease-free survival following brachytherapy

Reference	Setting	No of patients	Grade/stage	Treatment	Average age at diagnosis	Months followed
Kaye et al. (1995)	Minnesota (USA)	45	T1b = 2 T2 = 43 Gleason score <7 = 40PSA > 4 = 79%	Percutaneous ^{125}I implantation with and without EBRT	Mean = 71 years (50-83)	Mean = 24.2
Ragde et al. (1998)	Seattle (USA)	152	T1a–T3a (majority T2) PSA<4 = 38% 4-10 = 33% >10 = 29%	TRUS-guided ^{125}I implants (54/152 patients also received initial EBRT	Median = 70 years (range 53-92 years)	Median = 119 (range 3-134)
Stone and Stock (1999)	Mount Sinai Medical Center, New York	301	'Low risk': T2a or less, Gleason 6 or less, PSA 10 ng/mL or less = 36% 'Moderate risk': T2b-T2c, Gleason 7 or more, PSA 11-15 ng/mL = 51% 'High risk': T2c-T3c, Gleason 8 or more, PSA 16 ng/mL or more = 13%	Low risk: TRUS-guided implantation of ^{125}I Moderate risk: ^{125}I or ^{103}Pd (with and without 5 months hormonal therapy High risk: Brachytherapy, EBRT and 9 months hormonal therapy	Not reported	Low risk: median = 18 (range 12-84) Moderate risk: median = 27 (range 12-74) High risk: median = 13 (range 6-42)
Zelefsky et al. (1999)	Memorial Sloan-Kettering Cancer Center, New York	145 (compared with 137 patients treated with EBRT)	T1c = 68% T2a = 20% T2b = 12% PSA median = 6.1 ng/mL	CT planned trans-perineal ^{125}I implantation (compared with EBRT treatment group)	Median = 64 years	24 (range 6-103)

Table 9 Biochemical disease-free survival rates (measured by PSA) following brachytherapy

Primary author	Stage or grade	Definition of failure	2-year	3-year	4-year	5-year	10-year
Kaye et al. (1995)	T1b-T2	2 consecutive increases in PSA amounting to 2 ng/mL, PSA > 4 ng/mL, or post-treatment PSA> half pre-treatment PSA	97.7%				
Ragde et al. (1998)	T1a-T2c (majority T2)	PSA > 0.5 ng/mL				71%	66%
Stone and Stock (1999)	T2a-T3c (divided into low, moderate and groups)	2 PSA elevations above 1 ng/mL post treatment		patients: 71%	Low-risk patients (^{125}I alone): 91% Moderate-risk patients: brachytherapy with hormones = 85%, without hormones = 58%		
Zelefsky et al. (1999)	T1c-T2b	3 successive PSA elevations from post-treatment nadir				82%	

Table 10 Biochemical disease-free survival rates (measured by PSA) following radical prostatectomy

Primary author	Stage or grade	Definition of failure	5-year	7-year	10-year
Catalona and Smith (1994)	T1a-T2b	Presence of detectable PSA levels (> 0.6 ng/mL) or clinical detection	88%		
Oefelein et al. (1997)	Organ confined disease	Presence of detectable PSA levels	83%		53%
Ohori et al. (1994)	T1-T3	Progressive or sustained elevation of PSA greater than 0.4 ng/mL	94%		90%
Ramos et al. (1999)	T1a-T2c	The first detectable PSA greater than 0.3 ng/mL following surgery		84%	
Walsh et al. (1994)	T1-T2	Presence of detectable PSA levels			70%

Table 11 Biochemical disease-free survival rates (measured by PSA) following EBRT

Primary author	Stage or grade	Definition of failure	3-year	5-year	7-year	10-year
Leibel et al. (1994)	T1c-T3 (majority T2)	PSA > 4 ng/mL for 2 successive measurements	T1c-2a = 97% T2b = 86% T2c = 60%			
Zagars (1994)	T1-T2	Increasing PSA		66%		
Zelefsky et al. (1999)	T1c-T2b	3 successive elevations from post-treatment nadir		88%		
Zietman (1994)	T1a-T4	PSA > 4 PSA >1	T1-2 = 68% 49%			
Zietman (1994)		PSA > 1 ng/mL after 2 years		T1-2 = 66%		T1-2 = 47%

Figures 1–4: Biochemical survival rates after treatment for localised prostate cancer, D'Amico et al, 1998.

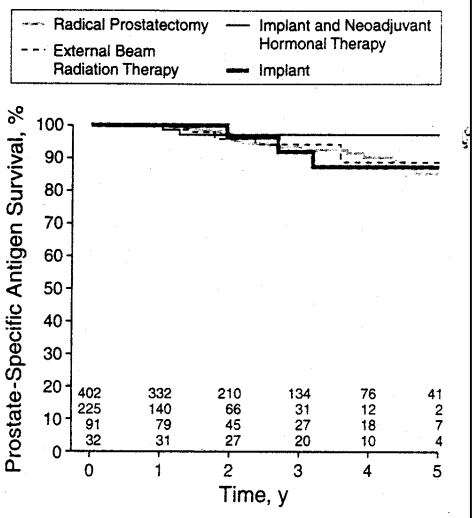

Figure 1.—Estimated prostate-specific antigen outcome for low-risk patients stratified by treatment modality. All pairwise *P* values are more than .25.

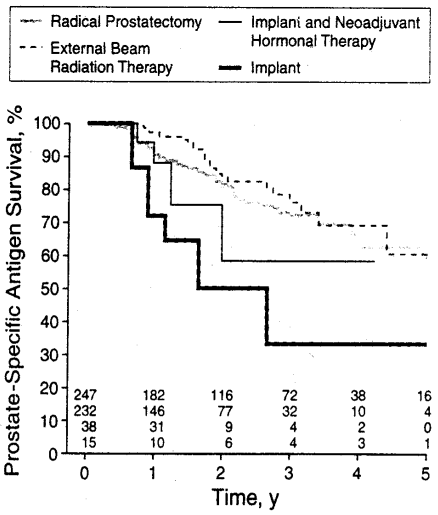

Figure 2.—Estimated prostate-specific antigen outcome for intermediate-risk patients. Pairwise *P* values are as follows: radical prostatectomy (RP) vs external beam radiation therapy (RT), .26; RP vs implant plus androgen ablation, .18; RP vs implant, .003; RT vs implant plus androgen ablation, .009; RT vs implant, .002; and implant plus androgen ablation vs implant, .14.

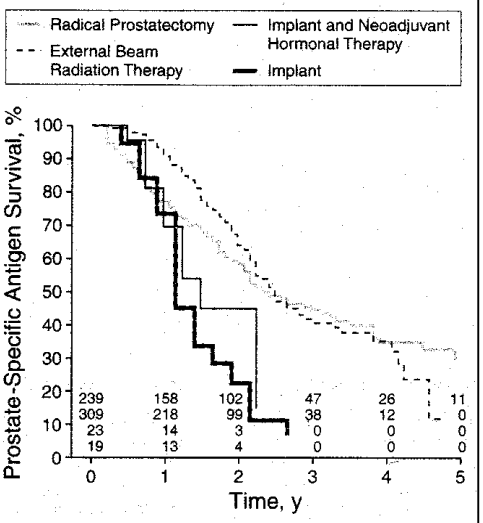

Figure 3.—Estimated prostate-specific antigen outcome for high-risk patients. Pairwise *P* values are as follows: radical prostatectomy (RP) vs external beam radiation therapy (RT), .25; RP vs implant plus androgen ablation, .01; RP vs implant, .005; RT vs implant plus androgen ablation, .007; RT vs implant, less than .001; and implant plus androgen ablation vs implant, .41.

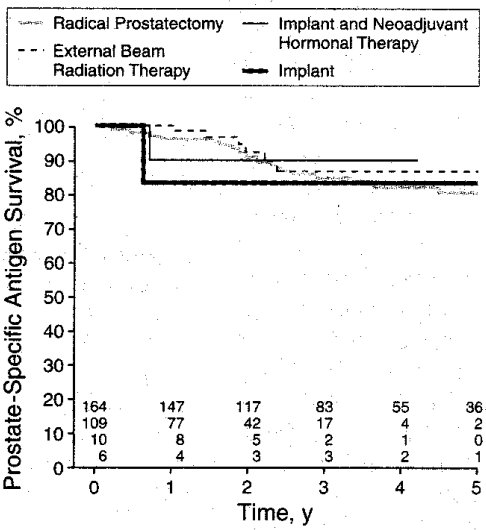

Figure 4.—Estimated prostate-specific antigen outcome for patients with biopsy Gleason score 2 through 4. All pairwise *P* values are more than .46.

Table 12 Cause-specific mortality from prostate cancer (T1–T2 patients only)

	Prostatectomy	EBRT	Brachytherapy	No active Rx
10 years	4-10%	14%	2%	10-14%
15 years	18-19%			19-25%

Prostatectomy — Frohmuller and Theiss 1995, Trapasso et al. 1994, Oefelein et al. 1997

EBRT — Hanks 1997

Brachytherapy — Ragde and Korb 2000

No active — Lu-Yao and Yao 1997, Johansson et al. 1997, Albertson et al. 1998

Note that the ranges reported in this table are the range of point estimates reported in the literature. The true value may therefore lie outside this range.

Discussion

Overview of methodological issues

The evaluation of the above studies presents particular difficulties and limitations to interpreting the data include:

- most of the studies identified have investigated only small groups of patients;
- because of recent changes in the technique, the time that patients have been followed-up with the current technique is limited;
- the studies have principally been conducted at specialised academic centres, which limits their generalisability;
- patients undergoing radiotherapy do not generally have surgical staging of their disease, which biases the staging of these patients and may potentially lead to an over-estimation of the relative effectiveness of radical prostatectomy;
- there was variability in the reporting of prognostic factors such as initial PSA levels;
- there is a differential selection of patients for radical prostatectomy and radiotherapy, with patients selected for radiotherapy commonly having a poorer prognosis and/or initial health status at the outset; and
- due to the age of the patients with this disease, there is a high rate of co-morbidity which increases the mortality from competing causes. This greatly complicates the calculation of survival data.

The overriding methodological issue is that it is difficult to compare the relative effectiveness of the various treatment options because of the heterogeneity of the patient populations and lack of comparable patient groups.

In the absence of a successful randomised controlled trial, conclusions about the relative effectiveness of brachytherapy compared with EBRT or prostatectomy must be based on only Level 3 or 4 evidence. The efficacy does appear to be dependent on the population group studied. The long-term consequences of the current brachytherapy techniques are also not well understood. The relative advantages of brachytherapy are its potential for potency preservation, its avoidance of the risks of surgery and the single session outpatient nature of the treatment.

The patients who appear to benefit most from brachytherapy are patients with low-volume, low-grade disease with a longer than 10-year life expectancy.

What are the economic considerations?

Brachytherapy has not been fully evaluated economically. The following table lists the economic considerations estimated by the applicant and the supporting committee. These comparative costings do not include the work-up before treatment started, or the potential costs of treating complications after treatment.

Table 13 Comparative costings of different treatment options

	Brachytherapy	Radical Prostatectomy	External Beam Radiotherapy
Pre-treatment prostatic ultrasound (TRUS)*	$100		
Computerised dosimetry (x2)*	$918		
Simulation and dosimetry*			$865
Days[1] in hospital @ $515 pd‡	$515	$3,090	
Operating Theatre‡	$1,000	$2,100	
Theatre Staff			
Urological surgeon‡	$995	$1,445	
Radiation Oncologist‡	$995	–	
Physicist	–	–	
Medical physicist‡?	–	–	
Anaesthetist‡	$114	$355	
Nursing staff‡	–	–	
Assistant	–	$238	
EBRT treatment @ $172.50 * (x35 treatments on average)†			$6,038
Disposables			
^{125}I seeds‡	$6,500	–	
Implant needles‡	$450	–	
Post-treatment check X-rays (x3)*			$446
Pathology‡	–	$250	
Pharmacy‡	–	$200	
Physiotherapy‡	–	$480	
TOTAL (medical costs)	$11,587	$8,158	$7,349

* Medicare Benefit Schedule Fee

† Estimate from expert committee

‡ Estimate from applicant

[1]Advanced surgery shared room

Before receiving brachytherapy, patients require a prostate TRUS volume study to determine the size and shape of the prostate and proximity to the bladder and rectum, and a seed position determination and evaluation of computer projected isodose curves (Ragde and Korb, 2000). The current Medicare Benefit Schedule Fee for this is $99.90. Both before and after implantation, brachytherapy patients require a computerised radiation dosimetry study, although only one study is claimable under current existing Medicare arrangements.

If about 20 per cent of patients with localised prostate cancer each year (800 patients a year in Australia) were to choose to have brachytherapy, the annual cost would be about $9,500,000. This would add $3,500 per patient, or $2,800,000 per annum to the cost of the same patients choosing prostatectomy.

This increase in direct costs needs to be weighed up against the possible reduction in complication rates, particularly impotence and sphincteric incontinence. The treatment of such complications is also expensive. Both the incidence and the cost of long-term complications from each of the treatments is highly uncertain. This results in it being extremely difficult to estimate the relative costs of the various treatments and their cost-effectiveness.

Brachytherapy also has lower indirect costs such as time off work. It can usually be performed as a day patient procedure and patients recover much faster than after prostatectomy.

The applicant has estimated that 20 per cent of patients with localised prostate cancer would elect to have brachytherapy and that the treatment would occur as a result of a substitution of treatment types, without substantially adding to the total number of patients being treated for localised prostate cancer. This estimate is, of course, uncertain. Any change in the usage of PSA screening for prostate cancer would also affect the cost of treating localised prostate cancer.

As explained above, the data on the rate of complications for each type of treatment are highly uncertain. This makes it difficult to estimate the relative costs of the various treatments and the potential cost implication of treating the complications of each.

Conclusions

Safety

The acute complications of brachytherapy are haematuria, dysuria, urinary obstructive symptoms, gastrointestinal complications and impotence. Late complications of brachytherapy could include urethral stricture, rectal irritation and impotence. While there are differences in the side effect profiles between the various therapies available, the overall incidence appears reasonably similar. However, brachytherapy could result in a higher rate of potency preservation than other forms of therapy for localised prostate cancer.

Effectiveness

There is limited information on the relative effectiveness of brachytherapy treatment. It can be considered as a first line treatment in those patients who are fully informed of the potential risks and benefits of each of the alternative treatments available. The ideal patient for brachytherapy is one with a low volume, low to intermediate grade disease and with a greater than 10-year life expectancy. It is contraindicated for patients with high grade tumours and those who have previously had a transurethral resection of the prostate.

Cost-effectiveness

A full economic evaluation of treatment options including work-up expenses and the costs of treating complications has not been undertaken. The estimated relative costs of brachytherapy, radical prostatectomy and radiotherapy in this report are based on information provided by the applicant and members of the supporting committee.

If approximately 20 per cent of patients with localised prostate cancer each year (800 patients a year in Australia) were to choose to have brachytherapy, the annual cost would be about $9,500,000. The additional cost compared with prostatectomy is about $3,500 per patient, or $2,800,000 per annum.

The direct costs of brachytherapy appear to be slightly higher than for other treatments of localised prostate cancer. However, these costs need to be weighed against the possibility that some complications of treatment occur less frequently. Indirect savings would also occur because patients require less time off work.

Recommendation

MSAC recommends that on the strength of evidence pertaining to brachytherapy for the treatment of prostate cancer (MSAC Application no. 1029), interim public funding should be supported for patients with prostate cancer meeting the following criteria:

- at clinical stages T1, T2a or T2b, 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 a life expectancy of more than 10 years; and
- where the treatment is conducted at approved sites.

This recommendation is to be reviewed no later than three years from the date of this report.

The Minister for Health and Aged Care accepted this recommendation on 9 February 2001.

Appendix A MSAC terms of reference and membership

The terms of reference of MSAC are to advise the Commonwealth Minister for Health and Aged Care 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;
- 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;
- 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
Professor David Weedon (Chair)	Pathology
Ms Hilda Bastian	Consumer health issues
Dr Ross Blair	Vascular surgery (New Zealand)
Mr Stephen Blamey	General surgery
Dr Paul Hemming	General practice
Dr Terri Jackson	Health economics
Professor Brendon Kearney	Health administration and planning
Mr Alan Keith	Assistant Secretary, Diagnostics and Technology Branch, Commonwealth Department of Health and Aged Care (from 3 May 1999)
Dr Richard King	Gastroenterology
Dr Michael Kitchener	Nuclear medicine
Professor Peter Phelan	Paediatrics
Dr David Robinson	Plastic surgery
Associate Professor John Simes	Clinical epidemiology and clinical trials
Dr Bryant Stokes	Neurological surgery, representing the Australian Health Ministers' Advisory Council (from 1 January 1999)
Dr John Primrose	Medical Adviser to MSAC

Appendix B Supporting committee

Supporting committee for MSAC application 1029
Brachytherapy for the treatment of prostate cancer

Dr Michael Kitchener (Chair) MBBS, FRACP Nuclear Medicine Specialist, Adelaide	MSAC member
Dr Ross Cartmill MBBS, FRACS, FRCS Consultant Urologist, Princess Alexandra Hospital, Brisbane	nominated by Royal Australasian College of Surgeons and the Urological Society of Australasia
Mr Clive Deverall Consumers Representative on the Department of Health and Aged Care's National Cancer Strategies Group	nominated by the Consumers' Health Forum of Australia
Dr Graeme Dickie MBBS, MBA, FRACP (nuclear medicine), FRANZCR (radiation oncology) Director of Radiation Oncology, Division of Oncology, Royal Brisbane Hospital	nominated by the Royal Australian and New Zealand College of Radiologists
Associate Professor Gillian Duchesne BSc (Hons), MD, MB, ChB, FRCR (London), FRANZCR Associate Professor, Monash University Principal Specialist (Radiation Oncology), William Buckland Radiotherapy Centre, Melbourne	nominated by the Royal Australian and New Zealand College of Radiologists
Dr Alastair Tulloch MB, ChB, FRCSE, FRACS Urological Surgeon, Perth Consultant Urologist, St John of God Health Care, Perth	nominated by the Urological Society of Australasia

Appendix C Studies examining the use of brachytherapy

Adolfsson et al. (1994)

This study examined the complications and 5-year survival rate of 37 patients who had been treated with ^{125}I implantation at Karolinska Hospital, Stockholm. At the time of follow-up, nine had died of prostate cancer. In addition, the rate of complications was high and in two cases led to the death of the patients. Because of the poor outcome and the high rate of complications the hospital had abandoned digitally directed retropubic ^{125}I implantation. This method of seed implantation is not used in Australia and the results of this study have not been included in the comparative results.

Benoit et al. (2000)

In 1991, 2124 men of the U.S Medicare population underwent prostate brachytherapy. A total of 176 men (8.3%) underwent a surgical procedure for bladder outlet obstruction during the follow-up period, including transurethral resection of the prostate in 141 men. Seven men (0.3%) underwent a colostomy for complications secondary to radiation, and four men (0.2%) had an artificial urinary sphincter placed after prostate brachytherapy. Penile prostheses were placed in 14 men (0.6%) in the first 24-36 months after prostate brachytherapy. A diagnosis of urinary incontinence was carried by 140 men (6.6%) after the procedure and 179 men (8.4%) carried a diagnosis of erectile dysfunction after their procedure. A diagnosis consistent with rectal injury secondary to radiation appeared in 116 men (5.5%) after prostate brachytherapy. The limitations of claim information in determining patient outcomes, however, must be kept in mind when evaluating these data.

Blasko et al. (1995)

This single-armed study examined the PSA-based, recurrence-free survival rate after ^{125}I implantation. One hundred and ninety-seven patients with moderately or well-differentiated tumours (T1-T2) underwent ultrasound-guided, transperineal brachytherapy and were followed-up for a median of three years (range 1-7 years). Pretreatment PSA levels were elevated in 138 (70%) of these. Among these patients, PSA level had decreased to less than 1.0 ng/ml in 97 per cent at 48 months after implantation. The actuarial rate of chemical or clinical failure at five years after treatment was 7 per cent, however there was a trend for higher failure rate among patients with higher initial PSA levels. No complications are discussed in this report. The authors conclude that brachytherapy is efficacious in patients with early-stage prostate cancer. The results of this study have not been included in the above tables because of the likelihood that there is some overlap between the patients reported in this series and those reported in Ragde et al. in 1997, 1998 and in Ragde and Korb 2000.

Catalona and Smith(1994)

Five-year disease recurrence rates (per PSA level) after prostatectomy were investigated in this study. Nine hundred and twenty-five consecutive men with clinical stage T1 2 disease underwent radical retropubic prostatectomy between 1983 and 1993 in St. Louis (USA). The overall rate of non-recurrence was 78 per cent, however the 5-year non-progression rate was higher in patients with non-palpable tumours detected using TURP (90%) and even higher for those non-palpable tumours detected via PSA levels alone (97%). This compares with a 5-year non-progression rate of 74% for palpable tumours. The average interval to cancer recurrence was 24 +/-21.5 months (range 1-101). Higher preoperative PSA levels were significantly associated with cancer recurrence. There was a lower rate of recurrence in patients with stage T1c than for patients with T1a or b, but this may be because of a shorter average follow-up period.

Critz et al. (1998)

This study examined the combination of brachytherapy and EBRT. Treatment results for men with prostate cancer staged by pelvic lymph node dissection were examined. Disease freedom was defined by a PSA nadir of 0.5 ng/ml or less. Three hundred and sixty-three men with clinical stage T1 or T2, node-negative prostate cancer were treated between 1984 and 1996 in Atlanta (Georgia) with a combination of retropubic ^{125}I prostate implant followed by EBRT. A further 657 men with the same stage disease were treated by transperineal implantation of ^{125}I followed by EBRT - making a total of 1,020 men. Average pre-treatment PSA was 10.5 ng/mL (range 0.3-188), and follow-up ranged from 1-14 years. Overall 5-year and 10-year disease-free survival rates were 79 and 72 per cent respectively, although trends in survival improved with lower initial PSA. Overall 5-year survival rates were significantly better for the ultrasound-guided technique than the retropubic approach - 92 and 73 per cent. With 10-year disease-free survival rates of 72 per cent, the authors conclude that combined EBRT and brachytherapy compares favourably with 10-year results for radical prostatectomy.

D'Amico et al. (1998)

This large study was one of the rare comparative ones and compared the biochemical outcome after brachytherapy, prostatectomy and EBRT for clinically localised prostate cancer. A total of 1872 patients were treated between 189 and 1987 at multiple centres in the USA for stage T1c-T2c tumours. Of these, 218 were treated with perineal template-guided ^{103}Pd implantation with and without androgen deprivation (median follow-up 41 months), 888 underwent radical retropubic prostatectomy and bilateral pelvic node sampling (median follow-up 38 months), and 766 underwent conformal EBRT (median follow-up 38 months). The authors report no statistical difference in 5-year PSA outcome for any treatment (with or without androgen deprivation) for patients in the low-risk group. Patients considered at intermediate or high risk of relapse were more likely to do so if treated with brachytherapy.

Grado (1998)

Grado (1998) evaluated the effectiveness and safety of transperineal ^{125}I brachytherapy guided by ultrasound and fluoroscope. Of 567 consecutive patients with biopsy proven prostate cancer at the Mayo Clinic Scottsdale between 1990 and 1996, 53 who had undergone prior radiation therapy for prostate or other pelvic cancer were excluded, and 24 were ineligible for brachytherapy, leaving 490 patients in the study. Seventy-two patients who had evidence of possible capsular involvement received adjunctive EBRT. Failure was established on the basis of all available clinical, imaging and biochemical evidence. Actuarial disease-free survival after 5 years was 79 per cent (95% CI, 71-85%) and actuarial rate of local control was 98 per cent (95% CI, 94-99%). Post-treatment PSA nadir and pretreatment PSA level were found to be significant predictors of disease-free survival. Few complications were found.

Kaye et al. (1995)

In this study, ultrasound or ultrasound plus fluoroscopic guidance was used for placement of ^{125}I in 132 patients between 1988 and 1993 in Abbott Northwestern Hospital, Minneapolis. Eight-six of these were followed-up for 11 months or more, and the 76 with clinically localised disease were the subjects of this study. Forty-five patients with tumours smaller than 2 cm in diameter and whose Gleason score was lower than 7 were treated with brachytherapy alone (group 1), while the remaining 31 received adjunctive EBRT (group 2). Complete clinical progression-free survival, including PSA, DRE and biopsy, was 51 per cent for group 1 and 63.3 per cent for group 2, for a mean follow-up of 26.3 months. PSA progression-free survival was 97.7 per cent for group 1 and 94.7 per cent for group 2.

Koutrouvelis (1998)

A total of 130 patients with localised disease underwent implantation with ^{103}Pd and ^{125}I seeds in Virginia using the 3-dimensional stereotactic posterior transischiorectal space, computerised tomography guided approach. This approach was selected because it is claimed to allow implantation irrespective of prostate size, urinary obstruction or TURP defects as well as for monitoring and correction of needle placement during the procedure. A decrease of PSA levels to below 2 ng/mL was reported in 95 per cent of patients by 24 months, and (although exact measures are not reported) successful initial results for patients with high grade tumours and high PSA levels were also reported. As well, the author reports that urinary obstruction improved in all patients and there was a relatively low complication rate. For instance, 95 per cent are reported to be free of erectile problems.

Leibel et al. (1994)

This study investigated the dose-escalation outcome of EBRT treatment in 324 patients with prostate cancer treated in the Memorial Sloan-Kettering Cancer Center in New York (USA). The patients were treated from 1988-1993, and while the stage of disease ranged from T1c-T3, more than 50 per cent were diagnosed with stage T2. Seventeen per cent also had androgen deprivation therapy to decrease prostatic volume. Complications were not given by type but only classified as gastrointestinal or genitourinary. Forty-three per cent of patients had Radiation Therapy Oncology Group (RTOG - a morbidity grading system) grade 2 or greater acute toxicity symptoms. In terms of late complications 6 of the 324 had Grade 2 or greater rectal complications and 9 had grade 2 or greater urinary complications. The 3-year actuarial probability of survival with a normal serum PSA level was 97 per cent for those with stage T1c-T2a, 86 per cent with stage T2b, 60 per cent with stage T2c and 43 per cent with stage T3 disease. An initial PSA of more than 20 ng/mL, a cancer stage higher than T2c and a Gleason score of more than 6 were found, by multivariate analysis, to be independently predictive of chemical relapse.

Oefelein et al. (1997)

This study investigated the long-term outcomes (median follow-up was 7 years) of prostatectomy in patients with high grade carcinoma. Five- and 10-year disease-free survival was determined after radical prostatectomy in 116 men Chicago (USA) with clinically localised but high grade prostate cancer (T1–T2). Ten-year disease-specific survival was 96 per cent for organ-confined disease, and 78 per cent for non-confined disease. Men with pelvic lymph node metastasis had a 55 per cent 10-year disease-specific survival. Five- and 10-year PSA progression-free survival was 83 per cent and 53 per cent respectively for localised disease, but the 5-year PSA progression-free survival in those with lymph node metastasis was only 33 per cent. The authors concluded that prostate cancer was the major cause of death, rather than competing causes, in men with high grade disease.

Ohori et al. (1994)

This study analysed a consecutive series of patients for survival after prostatectomy. Five hundred consecutive, eligible patients with T1-T3 disease underwent radical prostatectomy at the Methodist Hospital, Houston (Texas, USA). Survival was strongly associated with the grade of the tumour and whether the tumour was confined to the prostate gland. Overall the 5-year non-progression rate was 76 per cent. For patients with poorly differentiated tumours the non-progression rate at 5 years was 85 per cent, compared with 46 per cent for patients with cancer extending outside the gland. Impalpable tumours detected by an elevated PSA level were as likely to be poorly differentiated as palpable disease but were significantly more likely to be confined to the prostate.

Polascik et al. (1998)

This study compared prostatectomy recurrence-free survival rates (per PSA level) with data from an earlier single-arm study of recurrence-free survival for brachytherapy (Ragde et al. 1997). Seventy-six patients with T1-T2 disease underwent radical retropubic prostatectomy at the John Hopkins Hospital, Baltimore (USA) between 1988 and 1990. The patients were followed-up for a mean of 83.2 months (± 22.8 months). Actuarial 7-year progression-free survival (per PSA) for prostatectomy was 97.8 per cent compared with 79 per cent for brachytherapy (as reported by Ragde et al. (1997). The authors concluded that radical prostatectomy may be superior to brachytherapy for treating localised prostate cancer. However, they also stressed the need for caution in interpreting comparisons of results from single-arm studies that contain disparities in prognostic indicators such as stage, Gleason scores and pretreatment PSA levels.

Ragde et al. (1997)

One hundred and twenty-six consecutive patients (T1: 23%, T2: 77%) were treated with ^{125}I radionuclides in the period 1988–90 at Northwest Hospital, Seattle. Four patients who died within 1 year of implant (all had declining PSA levels and no evidence of clinical failure) were removed from the study, leaving 122. Mean follow-up was 69.3 months and pre-biopsy PSA values were available for all patients. PSA failure was defined by either two consecutive increases from nadir value, or failure to attain an arbitrary serum PSA value of 1.0 or 0.5 ng/ml at last follow-up. Seven-year survival was 77 per cent, the 7-year actuarial PSA progression free outcome 89 per cent, and PSA ≤ 1.0 ng/ml outcome 87 per cent. The authors noted that these biochemical outcomes were comparable to endpoints resulting from radical prostatectomy and EBRT.

Ragde et al. (1998)

One hundred and fifty-two consecutive prostate cancer patients (T1-T3) were treated in Northwest Hospital, Seattle, between 1987 and 1988. Ninety-eight received TRUS-guided ^{125}I brachytherapy, while the remaining 54 (classified as patients with higher risk according to clinical stage) also received EBRT. The median age of these patients was 70 years (range 53-92 years) and the median follow-up for all patients was 119 months (range 3-134 months). PSA failure was defined as PSA > 0.5 ng/mL, and clinical recurrence was determined by positive biopsy and/or radiographic evidence of metastases. The overall survival rate over 10 years was 65 per cent, with 64 per cent remaining clinically and biochemically free of disease at 10-year follow-up. By 10 years, there was no statistically significant difference in outcome for patients receiving brachytherapy alone or those who also received initial EBRT. The authors reported that pre-treatment serum PSA was the most accurate predictor of disease-free survival.

Ragde and Korb (2000)

This study re-presented the data from the 1998 study by the same authors (see above) with the addition of a review of the history of the development of brachytherapy and discussion of the latest implantation techniques. As the primary data presented in this review was unchanged from the 1998 report, the initial study only was included.

Ramos et al. (1999)

Ramot et al. compared prostatectomy recurrence-free survival rates (per PSA level) with data from an earlier single-arm study of recurrence-free survival for brachytherapy (Ragde et al. 1997). Two hundred and ninety-nine patients in Washington (USA) with T1-T2 stage disease underwent radical retropubic prostatectomy and were followed-up for a mean of 60 months (± 35 months). Mean 7-year recurrence-free survival for prostatectomy was 84 per cent compared with 79 per cent for brachytherapy (as reported by Ragde et al. (1997). The author concluded that prostatectomy was slightly more effective than brachytherapy, but not significantly so statistically. However, comparisons between the two studies may have been confounded by residual clinicopathological differences in tumours and different treatment endpoints.

Stock et al. (1996)

This study examined PSA, biopsy results and morbidity to evaluate the efficacy and safety of transperineal implantation guided by transrectal ultrasound. Ninety-seven newly diagnosed patients were implanted with ^{125}I (71 patients) or ^{103}Pd (26 patients) between 1990 and 1994 at Mount Sinai Hospital, New York. Patients who had prostate volumes greater than 55 cc were first given 3-months treatment of leuprolide and flutamide before receiving radiation therapy to hormonally downsize the tumour. These patients were implanted with ^{103}Pd. ^{103}Pd was also used for patients with Gleason scores of 7 or greater. Biochemical failure was defined as two consecutive increases in PSA levels above the nadir level, or, in those patients who were treated hormonally, a rise in PSA>1 ng/ml. Decreases in PSA often reach a nadir level by 18–24 months post implant. The later results from the same hospital (Stone and Stock 1999) have been included in this review.

Stone and Stock (1999)

This study evaluated the PSA outcome for 301 men in New York attending the Mount Sinai Medical Center. It studied patients with T1-T3 prostate cancer treated with either brachytherapy alone (for low-risk patients), brachytherapy with or without hormonal therapy (moderate-risk patients) or with a combination of brachytherapy, hormonal treatment and EBRT (patients with high risk). The study reports on the morbidity and freedom from chemical failure for each of the three categories of patients studied. The 3-year freedom from PSA failure for the high-risk group was 71 per cent, and the 4-year rate for the low-risk groups was 91 per cent. For the moderate-risk group, those undergoing hormonal treatment and brachytherapy achieved 85 per cent while those treated solely with brachytherapy only achieved 58 per cent by the 4-year point. The authors conclude that brachytherapy achieves comparable results to other treatments according to disease extent. They suggest that planning of treatment strategies using combinations of approaches according to disease extent is likely to produce improved results in more advanced disease.

Wallner et al. (1994)

This study evaluated short-term clinical and chemical disease progression after transperineal implantation of ^{125}I. CT scanning was used to plan the implantation. Sixty-two patients with clinical stage T1 or T2 prostatic carcinoma were treated at the Memorial Sloan-Kettering Cancer Centre between 1988 and 1991. Fifty-four patients had an elevated PSA before brachytherapy and no prior hormonal treatment, and 96 per cent of these had normal PSA within 24 months. Seven patients had disease progression. The actuarial chemical or clinical 3-year failure rate was 17 per cent. Eighty-one per cent of the 38 who were potent initially remained potent after 3 years. Eight per cent developed rectal ulcerations after 11-22 months and three required a TURP because of urinary symptoms.

Walsh et al. (1994)

This study reported on the experience at John Hopkins Hospital after 10 years of anatomical radical retropubic prostatectomy. Anatomical factors rather than the preservation of autonomic innervation were the major factors responsible for improved urinary control associated with an anatomical approach to radical prostatectomy. This series shows a generally improved rate of urinary continence after anatomical radical prostatectomy, and in the 8 per cent of patients for whom there were problems these were mostly mild. Of the 503 patients who were potent preoperatively and followed for a minimum of 18 months, 68 per cent were potent postoperatively. The three factors that were correlated with the return of sexual function were age, clinical and pathological stage, and preservation of the neurovascular bundle. There was also a significant improvement in the preservation of sexual function after the anatomical surgical technique was introduced. Case records were also checked against a self-completed questionnaire at 18-months post-surgery. Overall, the results were similar, but in 5 per cent of patients the case records stated that the patient was potent and the questionnaire stated that the patient was impotent and in 5 per cent the reverse was the case.

Zagars (1994)

This study looked at pre-treatment PSA and nadir PSA values as predictors of recurrent disease in men treated with EBRT. Between 1987 and 1991, 269 patients with clinical stage T1-T2 prostate cancer underwent EBRT at the Anderson Cancer Center (Houston, Texas) and were followed with serial PSA levels for a median of 30 months. Both pretreatment and nadir PSA values were highly significant as predictors of relapse. The nadir PSA value was achieved typically at 6-12 months. PSA values begin to increase approximately 4-5 years before the appearance of clinically overt disease. The 5-year actuarial rates of relapse or increasing PSA according to initial PSA were: 14 per cent for 4 ng/mL or less; 33 per cent for 4-10 ng/mL; 55 per cent for 10–30 ng/mL; and 80 per cent for greater than 30 ng/mL. Patients with a nadir PSA level of less than 1 ng/mL had a 12 per cent relapse rate at 5 years. Increases of nadir value were positively associated with relapse rates, with nearly two thirds of case with 4 ng/mL increases relapsing by 2 years.

Zelefsky et al. (1999)

This study compared PSA relapse-free survival and incidence of late toxicity for patients with early-stage disease undergoing transperineal implantation of ^{125}I and conformal EBRT. Of 282 patients with clinical stage T1c (55%) to T2b being treated at the Memorial Sloan-Kettering Cancer Centre between 1988 and 1995, 145 underwent brachytherapy and 137 underwent EBRT. Median pretreatment PSA levels were 6.1 ng/mL for brachytherapy and 6.6 ng/mL for EBRT with PSA 5-year actuarial PSA relapse-free survival rates of 82 and 88 per cent respectively. Protracted grade 2 urinary symptoms were more common for brachytherapy as was persistent grade 2 urinary toxicity (noted in 31%), which persisted for a median of 23 months. In contrast, acute grade 2 urinary symptoms were resolved in 4-6 weeks with EBRT. The 5-year likelihood of grade 2 late rectal toxicity for brachytherapy and EBRT was 11 and 6 per cent respectively, and the 5-year likelihood of erectile dysfunction was 53 and 43 per cent. The authors concluded that both treatments are effective for patients with early-stage prostate cancer, however persistent (albeit, eventually resolving) urinary toxicities are more prevalent for brachytherapy.

Zeitman (1994)

This study investigated PSA levels as a predictor of outcome after treatment with EBRT, with and without endocrine therapy. One hundred and sixty-one patients with stage T1-T4 tumours in Massachusetts General Hospital (Massachusetts, USA) were treated with a total of tumour dose of 68.4–72 Gy, using a 4-field technique between 1988 and 1992. Median follow-up was 32 months, with a range of 24-56 months. The authors reported that the likelihood of being free of biochemical relapse was a function of the initial PSA value. The authors conclude that an initial serum PSA level of more than 15 ng/mL is a strong predictor of probable failure with conventional radiation therapy. Post-treatment serum PSA monitoring is also a sensitive detector of early relapse.

Appendix D Recent health technology assessments of brachytherapy

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Abbreviations

CT	Computerised tomography (scan)
DRE	Digital rectal examination
GI	Gastrointestinal
GU	Genito-urinary
^{125}I	Iodine-125
MRI	Magnetic resonance imaging
PIN	Prostate intraepithelial neoplasia (cancer in situ)
PSA	Prostate specific antigen
SEER	Surveillance, Epidemiology and End Results (surveillance program - USA)
TNM	Grading and staging tumour classification system
TRUS	Transurethral ultrasound
TURP	Transurethral resection of the prostate

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