A systematic review of brachytherapy

Is it an effective and safe treatment for localised prostate cancer?

Jenny Doust, BMBS, FRACGP, is Senior Research Fellow, Centre for General Practice, University of Queensland.  
Emma Miller, RN, MPH, is Senior Project Officer, Communicable Disease Control Branch, Department of Human Services, South Australia.  
Gillian Duchesne, MD, FRANZCR, is Professor of Radiation Oncology, Peter MacCallum Cancer Institute, East Melbourne, Victoria.  
Michael Kitchener, MBBS, FRACP, is Senior Visiting Medical Specialist, Nuclear Medicine, Queen Elizabeth Hospital, Adelaide, South Australia.  
David Weller, PhD, FRACGP, is Professor, Department of General Practice, University of Edinburgh, Scotland.

BACKGROUND
Brachytherapy is a promising treatment for prostate cancer as it may have reduced rates of impotence and incontinence.

OBJECTIVE
General practitioners can influence the treatment patients receive by their referral patterns, so it is important they understand the effectiveness and safety of treatment. We reviewed the primary literature on brachytherapy as sole therapy for localised prostate cancer.

DISCUSSION
Although there have been many studies on the safety and effectiveness of brachytherapy, there have been no trials of brachytherapy versus other treatments that would control for factors such as tumour stage, grade, or initial prostate specific antigen levels. Brachytherapy for localised prostate cancer appears to have equivalent survival rates to surgery and lower rates of impotence and urinary incontinence.

The rate of diagnosis of prostate cancer has risen dramatically in Australia over the past 15 years, partly as a result of increased prostate specific antigen (PSA) testing. General practitioners play a key role in the referral of patients for treatment, and it is therefore important they are aware of the current evidence regarding the possible benefits and harms of the available treatment options.

Permanent brachytherapy is now available on the Medicare Benefits Schedule (MBS) for ‘low risk’ patients with clinically localised prostate cancer (stage T1, T2a or T2b, a PSA 10 ng/mL and a Gleason score of less than or equal to 6). In the United States, brachytherapy has become the most common form of treatment for localised prostate cancer, primarily due to the apparently lower risk of impotence and incontinence post-treatment. It also avoids the risks of surgery, and treatment can be performed as a day patient procedure with a shorter recovery time.

We reviewed the evidence on the effectiveness and safety of brachytherapy as a treatment for localised prostate cancer. The review was originally undertaken for the Medicare Services Advisory Committee as part of the listing process for the MBS. The full report is available on the MSAC website (http://www.health.gov.au/msac/reports.html).

Method
The medical literature was searched to identify relevant studies and reviews for the period between January 1990 and June 2002. Searches were conducted of the Cochrane Central Register of Controlled Trials, Medline, EMBASE and CancerLit databases. The search terms used were ‘prostate cancer’ or ‘prostatic neoplasm’ [MESH] and ‘brachytherapy’ or ‘iodine implant’ or ‘prostate implant’ or ‘brachytherapy’ [MESH]. Only articles published since 1990 were considered because of changes in technique at around that time. We only included studies of permanent seed implantation and excluded combination therapy with external beam radiotherapy or studies that included less than 40 patients.
The abstracts of all citations retrieved by the above searches were scanned and the full text of all studies that appeared to be primary studies obtained. The studies were assessed for quality and the data extracted independently by two reviewers. Any disagreements were resolved by consensus.

Results

Effectiveness

Until recently, there has been no agreement regarding the definition of failure after treatment for prostate cancer. All cause mortality may not accurately reflect the effectiveness of treatment because of the high rate of mortality from other causes in this older population. Common measures used are biochemical failure (indicated by rising PSA levels) or disease free survival (no biochemical or clinical evidence of disease), but the way that these are defined has varied considerably between the studies.

We identified two systematic reviews,7,8 seven retrospective cohort studies,9-15 and 22 case series16-32 that reported survival rates following brachytherapy. Twenty-three studies involved reports on overlapping or duplicate cohorts of patients. There have been no trials comparing brachytherapy with other modalities or against deferred initial treatment. (A trial of prostatectomy versus brachytherapy in low risk men has commenced in the United States and Canada [SPIRIT trial],2 but will not report for a number of years). The results are shown schematically in Figure 1. The effect of potential confounding factors such as age, stage of disease, and pre-treatment PSA levels result in the wide range of results seen in these uncontrolled studies, but they show that survival rates are generally high for all treatment modalities for patients with low risk disease.

The retrospective cohort study by Brachman et al.7 illustrates the dangers of comparisons between studies without adjusting for confounding factors. This study showed similar rates of survival following brachytherapy and external beam radiotherapy (EBRT) overall, but patients treated with brachytherapy had lower initial PSA and Gleason scores. When the results were analysed by presenting PSA and Gleason score, patients with a presenting PSA >10 or a Gleason score >6 had lower survival rates when treated with brachytherapy than when treated with EBRT. The difference in survival rates between low, intermediate and high risk groups was confirmed by another retrospective cohort analysis.4 This study found no difference in biochemical progression free survival rates between patients treated with radical prostatectomy, EBRT or brachytherapy for patients defined as low risk (stage T2a, PSA 10 ng/mL and Gleason score 6) but lower survival rates for patients at intermediate or high risk treated with brachytherapy than for those treated with surgery or EBRT. The results of these two studies conflict with a more recent study that showed no difference in survival between men treated with brachytherapy or radical prostatectomy even in intermediate and high risk groups.9

Survival rates for all treatment modalities are high for all men and all treatments in the low risk group (>90%). This raises the question, is brachytherapy – as has been suggested previously – an expensive form of ‘watchful waiting’?33 Ideally survival should be compared to that of a group treated with deferred initial treatment and should define the proportion and the characteristics of men who require intervention. About 50% of men on waiting programs come to active treatment within 5 years, so it is the effects of delayed treatment rather than avoidance of
treatment that should be analysed.34

Safety

We identified two systematic reviews,23 one randomised controlled trial of iodine versus palladium implants,28 one prospective cohort study,26 seven retrospective cohort studies,32,36-41 and 27 case series10,32,42-46 that reported on complications following brachytherapy. As with the studies of effectiveness, there were several reports of overlapping and duplicate cohorts of patients. The complication rates reported in the literature are shown schematically in Figure 2. Many report complications according to the Radiation Therapy Oncology Group (RTOG) toxicity scales (Table 1).

It is difficult to compare populations with varying times of observation since complication rates vary considerably over time. This causes some of the variation seen in Figure 2. In the immediate post-treatment period, the most common complication is acute urinary retention, which may require temporary catheterisation. This occurs in about 15% of patients,47,50 with one study reporting the rate to be as high as 38%.51 It has been shown that up to 1% of seeds migrate to the lungs as shown on chest X-ray, but there are no known harmful side effects from this.43,52 Urinary symptoms such as frequency, nocturia and dysuria occur commonly and rise to a peak of about 80% of patients complaining of symptoms 2–3 months after treatment and then declines.32,45

Later complications of brachytherapy include urethral stricture, impotence and incontinence. The median time to the development of a stricture has been reported as 18 months29 and 27 months.52 Approximately 7% of Medicare patients in the United States who had had brachytherapy treatment required a later TURP for obstruction29,50 which is consistent with the rate of strictures reported in case series.15,32,52 The median time to impotency was 14 months.53 Generally, there have been lower rates of impotence reported after brachytherapy, but this finding is not consistent and a recent study found worse sexual functioning in men treated with brachytherapy than with EBRT or prostatectomy.28 Figure 2 shows the wide range of rates of impotency reported from case series. Higher rates of impotence are seen in studies with an older

![Figure 2. Complications following treatment for clinically localised prostate cancer (measured at 12-24 months post-treatment)](image)

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<th>Table 1. Modified RTOG toxicity scales55,57</th>
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average age of patients and where self reports from patients were used rather than case records. Incontinence has also been recorded as a complication in several studies, but this has mainly occurred in patients who have had a TURP either prior to or after brachytherapy. A much higher rate was seen, however, in a study using self reporting from patients. Comparisons with EBRT have generally shown fewer grade 2 and grade 3 urinary and rectal symptoms. The presence of complications does not necessarily give a good indication of how severely men’s lives are disrupted by these problems. A survey of men treated for clinically localised prostate cancer as part of the Health Professional Study found that men treated with brachytherapy had better sexual function and bother scores and urinary function scores but worse urinary bother, bowel function and bowel bother scores than men treated with prostatectomy.

Discussion

The decision facing a man recently diagnosed with clinically localised prostate cancer is one of the most difficult in medicine. The decision is subject to a trade-off between the possible survival advantage of treatment against the quality of life issues that are associated with treatment, and yet we have few high quality studies to determine the harms and benefits with any certainty. General practitioners need to be able to assist men with this choice, including the choice of referral options.

Radical prostatectomy is the most established treatment for localised prostate cancer in Australia, but there is still only limited high level evidence regarding its effectiveness. A recent Scandinavian trial of radical prostatectomy versus ‘watchful waiting’ showed that surgery reduced disease specific mortality but not overall mortality. A trial is also underway in the United States to assess the effectiveness of radical prostatectomy versus initial observation for clinically localised prostate cancer (PIVOT trial), but the results of this trial will not be available for several years. Based on the available data, the incidence of complications appears to be similar for the three main treatment options. Brachytherapy may have some advantage in terms of potency preservation and preservation of urinary continence but has a higher incidence of obstructive urinary symptoms and irritative urinary symptoms, at least in the short term. In terms of treatment modality, brachytherapy as sole treatment is really only applicable to patients with disease that is truly likely to be organ confined (see the MSAC criteria), as occult spread beyond the gland would not be effectively treated. For this group of patients, given that the evidence suggests similar outcomes for the different modalities, patients may be advised to make their decision based on the side effect profiles of the treatments.

General practitioners need to ensure that their patients are getting the best advice available so that patients can make an informed decision regarding treatment.

One resource that may be of assistance is the Prostate Cancer Consumer Guide produced by the Australian Cancer Network and available from the Cancer Council in each state.

Summary of important points

- Brachytherapy appears to be as effective as prostatectomy for men with ‘low risk’ localised prostate cancer, but there have been no studies to demonstrate whether it has better survival rates than ‘watchful waiting’.
- Brachytherapy generally results in lower rates of impotence and incontinence than surgery or EBRT but higher rates of obstructive and irritative urinary symptoms.
- Permanent brachytherapy is available on the MBS for ‘low risk’ patients with clinically localised prostate cancer (stage T1, T2a or T2b, a PSA 10 ng/mL and a Gleason score 6).

References


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Correspondence
Email: j.doust@sph.uq.edu.au