Systematic overview of the evidence for brachytherapy in clinically localized prostate cancer

Crook J, Lukka H, Klotz L, Bestic N, Johnston M

Authors' objectives
To examine the role of brachytherapy (permanent seed implantation) in treating clinically localised (T1 and T2) prostate cancer.

Searching
MEDLINE and Cancerlit were searched from 1988 to April 1999 using the terms 'prostate cancer', 'prostate neoplasm', 'brachytherapy', 'seed implant', 'interstitial radiotherapy', 'practice guideline', 'meta-analysis', 'randomized clinical trial' and 'clinical trial'. Studies reported as abstracts were excluded from the review. The web-based version of this review reported that it is currently being updated using the following searches: MEDLINE from April 1999 to May 2001; Cancerlit from April 1999 to March 2001; the Cochrane Library (Issue 2, 2001); and the PDQ database.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) that compared brachytherapy with standard treatment were eligible for inclusion in the review, but none were found. Therefore, prospective studies (e.g. case series and cohort studies) were included.

Specific interventions included in the review
Prostate brachytherapy using permanent implantation with radioactive seeds (iodine-125 or palladium-103). Studies were eligible for inclusion if brachytherapy was performed under ultrasound or computed tomography guidance. Brachytherapy was examined alone, or compared with brachytherapy plus external beam therapy.

Participants included in the review
Men with clinically localised (T1 or T2) prostate cancer. Data on their age were not reported.

Outcomes assessed in the review
To be eligible for inclusion, outcome data had to be reported in terms of the rates of freedom from biochemical failure (biochemically no evidence of disease, bNED), biopsy results or toxicity (acute and chronic).

How were decisions on the relevance of primary studies made?
The evidence was selected and reviewed by one member of the Cancer Care Ontario Practice Guidelines Initiative's Genitourinary Cancer Disease Site Group.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

In the paper and web version of the review, the data extracted and tabulated included: study type; study identification; sample size; tumour stage and Gleason score with group size; the median follow-up in months; the rate of freedom from failure or disease-free survival; and negative biopsy result.

Methods of synthesis
How were the studies combined?
A narrative synthesis was undertaken. The studies were grouped by treatment regime (brachytherapy alone, brachytherapy following external beam radiotherapy, and brachytherapy preceding external beam radiotherapy), and by outcome within these groups (bNED rate, biopsy results, and toxicity).

How were differences between studies investigated?
The results were discussed in light of differences between the study participants, e.g. tumour stage, Gleason score and serum prostate-specific antigen (PSA) level.

Results of the review
Sixteen studies were included in the review: 13 case series and 3 cohort studies; the overall sample size was not reported in the original review. In the web-based version of the review, there were 17 studies (14 case series and 3 cohort studies) with 2,814 evaluable participants (2,520 in the case series, and 294 in the cohort studies). The authors state that it is unclear whether the same patients were included in the case series conducted at the same centres (for brachytherapy alone) but published as separate studies.

Brachytherapy administered alone. Ten case series and one cohort study examined brachytherapy alone. Six of the case series and the cohort study reported on bNED rates. The rates varied considerably from one series to another, e.g. at a median follow-up of 36 months, one study reported a 5-year actuarial bNED rate of 93% for 197 patients, while another study reported a 4-year actuarial bNED of 63% for 92 patients. This variation was largely due to differences in the patient selection criteria. Pre-treatment PSA and tumour stage were also important predictors of outcome. Seven case series reported biopsy results. However, case selection and difficulties in obtaining biopsy specimens made the comparison of results difficult. Potential adverse effects of brachytherapy included acute irritative or obstructive urinary symptoms (46 to 54% of the patients), acute urinary retention (1 to 14%) and acute proctitis (1 to 2%). Chronic adverse events included urinary incontinence (5 to 6%, compared with 13% after undergoing a transurethral resection of the prostate), haematuria (1 to 2%), strictures (1 to 2%), proctitis (1 to 3%) and impotence (4 to 14%).

Brachytherapy following external beam radiotherapy.
Two case series and two cohort studies examined brachytherapy following external beam radiotherapy (only one case series was presented in the original review). Despite the selection of less favourable tumours for combined treatment (45 Gy in 25 fractions plus brachytherapy with iodine seeds), there was a trend toward improved bNED rates with combined treatment when compared with brachytherapy alone. One study reported positive biopsy results (at median 55 months), while another reported no difference in positive biopsy rates between the combined treatment group and the brachytherapy group. The most commonly reported adverse effects were diarrhea and dysuria (88% patients had grade 1 and 2 symptoms, 3% had grade 3), rectal pain or tenesmus (55%), and persistent urinary retention (21%). Other symptoms included nausea (15%), urinary incontinence (9%), urinary tract infection (6%), haematospermia (15%), and persistent perineal pain (12%). Chronic toxicity was not well described. One study reported 18% impotence at one year and 23% at two years.

Brachytherapy preceding external beam radiotherapy.
Two case series reported on brachytherapy preceding external beam radiotherapy, only one of which reported the bNED rate (92% at 5 years). The other study only reported biopsy data: in this study, 48% of the patients had positive biopsy results. Adverse results were reported in one case series: 75% experienced mild and transient cystitis or diarrhea. Rectovesical fistula occurred in 6% of patients, anal ulcer in 3%, haemorrhagic proctitis in 16%, and severe persistent cystitis in 25%.

Authors' conclusions
In the original review, the authors concluded that there was insufficient evidence to recommend the use of brachytherapy over current standard therapy for localised prostate cancer. Brachytherapy using transrectal ultrasound guidance for seed implantation is promising in terms of freedom from biochemical failure in selected patients with early-stage prostate cancer. The spectrum of adverse effects associated with brachytherapy differs from that associated with external beam radiotherapy. Acute urinary symptoms tend to be more prolonged and more severe with brachytherapy. When brachytherapy is combined with external beam radiotherapy, the potential toxicity is additive. In
the web-based version of the review, it is stated that the Genitourinary Cancer Disease Site Group is reviewing new evidence.

**CRD commentary**
This review is regularly updated (see Other Publications of Related Interest). In the current web-based version of the review, there is one more paper than in the original review, but this has not changed the interpretation of the results. The review question and inclusion and exclusion criteria were clearly defined. In the original review, the search was conducted on only two databases, and there was no evidence of a search for unpublished data or for studies published in languages other than English. It is possible, therefore, that some studies may have been missed.

The authors do not report a method for assessing validity, and it appears that only one reviewer selected and extracted the studies. Details of the individual studies have been presented in the web-based version of the review, although some information is lacking (e.g. age of the participants). The studies have been summarised appropriately as a narrative, and the authors have discussed sources of heterogeneity between the studies.

The authors’ conclusions are appropriately cautious, but would have been strengthened by an assessment of the quality of the studies.

**Implications of the review for practice and research**
Practice: The authors state that brachytherapy should be available to selected patients (those with T1c or T2a tumours, a Gleason score of 6 or lower, and a serum PSA level of 10 microg/L or less), after discussion of the available data and potential adverse effects.

Research: The authors state that brachytherapy is currently available outside of clinical trials, but whenever possible, patients should be asked to participate in randomised trials comparing brachytherapy and current standard therapy.

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**Other publications of related interest**
This paper is based on a Practice Guideline/Evidence Summary report produced by Cancer Care Ontario Practice Guidelines Initiative. The series is published on the Internet and regularly updated. To ensure that you are viewing the most up to date version, go to the Cancer Care Ontario website at: http://www.cancercare.on.ca/english/toolbox/qualityguidelines/pebc/ This abstract is based on the journal article and web version accessed on 05/06/2002.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.