

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

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## Abstract

**Background:** Brachytherapy (permanent implantation of radioactive seeds) has emerged as an alternative to existing standard therapy with radical prostatectomy or external beam radiotherapy in the treatment of clinically localized (T1 and T2) prostate cancer. The Genitourinary Cancer Disease Site Group of the Cancer Care Ontario Practice Guidelines Initiative examined the role of brachytherapy in treating clinically localized prostate cancer.

**Methods:** A systematic review of articles published from 1988 to April 1999, retrieved through a search of MEDLINE and CANCERLIT databases, was combined with a consensus interpretation of the evidence in the context of conventional practice.

**Results:** Although there were no randomized trials comparing brachytherapy with standard treatment, evidence was available from 13 case series and 3 cohort studies. Rates of freedom from biochemical failure (biochemically no evidence of disease [bNED]) varied considerably from one series to another and were highly dependent on tumour stage, grade and pretreatment serum prostate-specific antigen (PSA) levels. Results in patients with favourable tumours (T1 or T2 tumour, Gleason score of 6 or lower, serum PSA level of 10 ng/mL [ $\mu\text{g/L}$ ] or less) were comparable to those in patients undergoing radical prostatectomy. Acute urinary retention was reported in 1%–14% of patients. Long-term sequelae occurred in less than 5% of patients and included urinary incontinence, cystitis, urethral strictures and proctitis. Sexual potency was maintained after implantation in 86%–96% of patients.

**Interpretation:** At present, there is insufficient evidence to recommend the use of brachytherapy over current standard therapy for localized 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. Brachytherapy is currently available outside of clinical trials, but whenever possible patients should be asked to participate in randomized trials comparing brachytherapy and current standard therapy. 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  $\mu\text{g/L}$  or less), after discussion of the available data and potential adverse effects.

Otherwise healthy men with clinically localized prostate cancer have a choice of therapies. Although both radical prostatectomy and external beam radiotherapy have a risk of significant long-term morbidity, patients with low-risk prostate cancer have excellent 5-year biochemical progression-free rates with these standard therapies: 85%–96% after radical prostatectomy<sup>1–3</sup> and 81%–94% after external beam radiotherapy.<sup>1,4,5</sup> Given the long survival times of this population, biochemical freedom from relapse (bNED) is widely accepted as both appropriate and practical as a surrogate endpoint for ultimate cancer control.

Brachytherapy (permanent implantation of radioactive seeds in the prostate) (Fig. 1) is not new. In the 1970s and early 1980s, retropubic implantation of iodine 125 seeds

## Research

## Recherche

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was an attractive alternative to external beam radiotherapy for localized prostate cancer because of its ability to deliver a much higher dose of radiation. Unfortunately, 15-year follow-up data indicated that only 21% of patients were free of local failure.<sup>6</sup> The free-hand technique used then to guide implantation is now recognized as being suboptimal (Table 1).

Modern brachytherapy, using either iodine 125 or palladium 103 seeds, is performed under the guidance of transrectal ultrasonography (TRUS) and is planned and evaluated using 3-dimensional computer software. Promising early results, a minimally invasive technique and rapidity of the outpatient procedure have made brachytherapy an attractive alternative to radical prostatectomy and external beam radiotherapy for localized prostate cancer. Although widely available and popular in the United States, brachytherapy has only recently become available in Canada.

The Genitourinary Cancer Disease Site Group of the Cancer Care Ontario Practice Guidelines Initiative conducted a systematic review of the literature to clarify the role of brachytherapy in treating clinically localized (T1 and T2) prostate cancer. The group comprises urologists, radiation oncologists, medical oncologists, a pathologist and 2 community representatives.

## Methods

A systematic search of the MEDLINE and CANCELIT databases was carried out for articles published from 1988 to April 1999 using the search terms "prostate cancer," "prostate neoplasm," "brachytherapy," "seed implant," "interstitial radiother-

apy," "practice guideline," "meta-analysis," "randomized clinical trial" and "clinical trial." No randomized trials comparing brachytherapy with standard treatment were found. Relevant articles evaluating permanent seed implantation for clinically localized prostate cancer were reviewed. Articles had to meet the following criteria: series limited to T1 or T2 prostate cancer (Appendix 1); brachytherapy performed under ultrasound or CT guidance; outcome data reported in terms of freedom from biochemical failure (bNED [biochemically no evidence of disease]), biopsy results or toxicity; and report not published as an abstract.

Although survival is the ultimate and irrefutable measure of successful treatment of cancer, the long natural history of prostate cancer promotes the use of surrogate endpoints such as the serum prostate-specific antigen (PSA) level and post-treatment biopsy results. These endpoints antedate clinical progression and ultimate death from prostate cancer by years and thus permit more rapid evaluation of treatment efficacy. Their use, however, is not without controversy.

The 1997 publication of the American Society for Therapeutic Radiology and Oncology consensus guideline<sup>8</sup> provided criteria for defining biochemical failure after radiotherapy. Before this guideline, many different definitions of PSA failure were used, based either on a threshold<sup>9,10</sup> or on consecutive rises in PSA level.<sup>11-13</sup>

Biopsy after radiotherapy is not routinely used and is associated with problems of false-positive and false-negative results and of patient selection bias. Biopsy status cannot be considered a "gold standard" of treatment efficacy.

Evidence was selected and reviewed by a member of the Genitourinary Cancer Disease Site Group. The group reviewed and discussed a draft of the evidence summary. The final version was approved by the group and the Practice Guidelines Coordinating Committee of Cancer Care Ontario.<sup>7</sup>

## Results

The following studies were reviewed: 10 case series and 1 cohort study of brachytherapy alone; 1 case series of external beam radiotherapy followed by brachytherapy as a boost, and 2 cohort studies comparing this combination with brachytherapy alone; and 2 case series of brachytherapy followed by external beam radiotherapy.

### *Brachytherapy alone*

Results from 6 case series<sup>9-12,14,15</sup> are summarized in Table 2. Rates of freedom from biochemical failure (bNED) varied considerably from one series to another, from 63% at 4 years ( $n = 92$ )<sup>15</sup> to 93% at 5 years ( $n = 197$ ).<sup>12</sup> This variation was largely due to differences in patient selection criteria.

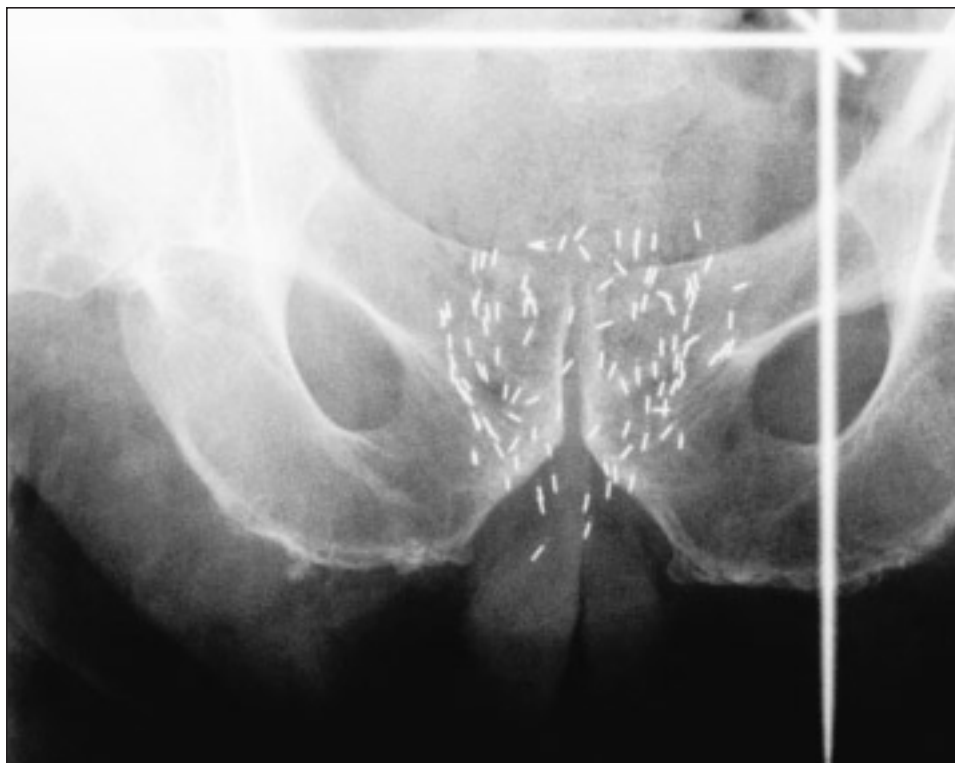


Fig. 1: Anteroposterior radiograph, showing radioactive seeds implanted into prostate gland.

**Table 1: Brachytherapy technique used in the 1970s at the Memorial Sloan-Kettering Cancer Center<sup>6</sup> and current TRUS-guided brachytherapy technique**

Component	Technique in 1970s	Current technique
Planning	Nomogram based on prostate size determined amount of radioactivity to be used	3-Dimensional computer planning determines precise location of each seed, not simply overall number of seeds
Placement of seeds	Open procedure with retropubic exposure of prostate. Operator attempted to distribute seeds evenly using free-hand approach	Closed procedure with preloaded needles inserted transperineally under TRUS guidance. Template ensures parallel position of rows of seeds, and TRUS determines correct depth of insertion
Evaluation after implantation	None	CT-based dosimetry 1 mo after implantation allows calculation of rectal and urethral doses and confirms that required dose is received by entire prostate

Note: TRUS = transrectal ultrasonography.

**Table 2: Case series of brachytherapy alone that reported rates of freedom from biochemical failure**

Case series	No. of cases	Tumour stage,*	Gleason score, group size	Median follow-up, (and range), mo	Rate of freedom from failure, %
D'Amico et al <sup>1</sup>	68	T1-T2a	2-4: 6 5-6: 47 7-10: 13	60	bNED (5-yr): 88
Ragde et al <sup>9</sup>	126	T1a: 5 T1b: 4 T1c: 19 T2a: 76 T2b: 17 T2c: 1	2-4: 61 5-6: 61	69	bNED (7-yr): 89
Beyer and Priestley <sup>10</sup>	489	T1a: 64 T2a: 260 T2b: 117	2-4: 106 5-6: 306 7-10: 61	34 (3-70)	bNED (5-yr) Gleason 2-4: 86 Gleason 5-6: 63 Gleason 7-10: 32
Stokes et al <sup>11</sup>	142	T1b: 13 T1c: 8 T2a: 63 T2b: 46 T2c: 12	≤ 7: 142	30 (12-72)	NED (overall): 76
Blasko et al <sup>12</sup>	197	T1b: 5 T1c: 33 T2a: 139 T2b: 21	2-4: 105 5-6: 87	36 (12-84)	bNED (5-yr): 93 T1b: 100 T1c: 92 T2a: 95 T2b: 81
Stock et al <sup>14</sup>	97	T1b: 4 T1c: 9 T2a: 22 T2b: 52 T2c: 10	2-4: 31 5-6: 49 ≥ 7: 17	18 (6-51)	bNED (2-yr): 76 T1b-T2a: 91 T2b/T2c: 69
Wallner et al <sup>15</sup>	92	T1: 34 T2: 58	2-4: 27 5-7: 64	36 (12-84)	bNED (4-yr): 63

Note: bNED = biochemically no evidence of disease (non-rising serum prostate-specific antigen [PSA] level), NED = no evidence of disease (biochemical or clinical).

\*See Appendix 1 for definitions of tumour stages.

Beyer and Priestley<sup>10</sup> reported the largest case series (*n* = 489) and elucidated the main prognostic factors for freedom from biochemical failure. Their series, and others, have documented decreasing 5-year actuarial bNED rates with increasing Gleason scores,<sup>16</sup> higher pretreatment PSA levels (Table 3) and increasing tumour stage. bNED rates of 90%–94% have been reported for T1 tumours, 70%–75% for T2a tumours and 34% for T2b and T2c tumours.<sup>10,11</sup>

D’Amico and associates<sup>1</sup> described 68 patients who received <sup>103</sup>Pd seed implants as part of a cohort study comparing brachytherapy, external beam radiotherapy and radical prostatectomy. The known prognostic variables (tumour stage, serum PSA level and Gleason score) were combined to create low-, intermediate- and high-risk groups. For low-risk patients (T1c or T2a tumour, Gleason score of 6 or lower, and serum PSA level of 10 ng/mL [μg/L] or less) the 5-year bNED rate was 88% (28/32). For those at intermediate risk (T2b tumour, Gleason score of 7 and serum PSA level greater than 10 μg/L) the bNED rate fell to 33% (5/15). For the high-risk patients (T2c tumour, Gleason score greater than 7 and serum PSA level greater than 20 μg/L) the rate was 0% (0/19) at 3 years.

**Table 3: Range of biochemical disease-free rates according to pretreatment serum PSA levels**<sup>10,11,15</sup>

Pretreatment serum PSA value, μg/L	Disease-free rate, %
≤ 4	93–100
4.1–10.0	70–86
> 10.0	39–49

Seven case series reported biopsy results.<sup>9,11,13,14,17–19</sup> Table 4 provides negative biopsy rates for 4 of these series.<sup>9,13,14,19</sup> Case selection and difficulties in obtaining biopsy specimens make comparison of the results difficult. Prestidge and associates<sup>13</sup> and Ragde and associates,<sup>9</sup> reporting from the same centre, found positive biopsy results in 3%–5% of cases and negative results in 80%–82% of cases; the remaining results were indeterminate. Others<sup>14,18</sup> reported positive biopsy results in 16%–26% of cases at 18–36 months after brachytherapy.

Potential adverse effects of brachytherapy are summarized in Table 5. About 50% of patients experienced acute irritative or obstructive urinary symptoms requiring drug treatment,<sup>15,17</sup> which persisted in 29% of patients at 12

**Table 5: Potential adverse effects of brachytherapy**

<b>Acute (&lt; 12 mo)</b> <sup>11,12,14,15,17,18</sup>
Irritative urinary symptoms (grade 1–2*): 46%–54% of patients
Urinary retention: 1%–14%
Proctitis: 1%–2%
<b>Chronic (&gt; 12 mo)</b> <sup>9,10,12,15</sup>
≥ grade 2* urinary symptoms: 29% at 12 mo, 14% at 24 mo
Incontinence: 5%–6%
Incontinence after TURP: 13%
Hematuria: 1%–2%
Stricture: 1%–2%
Proctitis: 1%–3%
Impotence: 4%–14%

Note: TURP = transurethral resection of the prostate.  
\*Grade 1 = minor, requiring no treatment; grade 2 = responding to simple outpatient management; grade 3 = distressing, altering lifestyle, and requiring minor surgery or admission to hospital.

**Table 4: Case series of brachytherapy alone that reported biopsy results**

Case series	No. of cases	Tumour stage, group size	Gleason score, group size	Median follow-up, (and range), mo	Negative biopsy rate, % (and no. of cases)
Ragde et al <sup>9</sup>	126	T1a: 5 T1b: 4 T1c: 19 T2a: 76 T2b: 17 T2c: 1	2–4: 61 5–6: 61	69	82 (63/77)
Prestidge et al <sup>13</sup>	402	T1a: 8 T1b: 11 T1c: 88 T2a: 250 T2b: 40 T2c: 6	2–4: 158 5–6: 199 ≥ 7: 37	40 (12–83)	80 (161/201)
Stock et al <sup>14</sup>	97	T1b: 4 T1c: 9 T2a: 22 T2b: 52 T2c: 10	2–4: 31 5–6: 49 ≥ 7: 17	18 (6–51)	74 (29/39) at 18–36 mo
Vijverberg et al <sup>19</sup>	52	T0: 1 T2: 23 T2–3: 21 T3: 1		30 (16–64)	22 at 6 mo

months and in 14% at 24 months.<sup>15</sup> Acute urinary retention was reported to occur in 1%–14% of patients<sup>11,12,15,17</sup> and proctitis in 1%–2%.<sup>11,12,14,18</sup> Urinary incontinence was present in 5%–6% of patients<sup>9,10,12</sup> but was much more common (13%) after transurethral resection of the prostate (TURP).<sup>9</sup> Potency<sup>14,15</sup> was maintained in 86%–96% of patients at 2–3 years after implantation.

### Brachytherapy following external beam radiotherapy

Despite selection of less favourable tumours for combined treatment (45 Gy in 25 fractions plus brachytherapy with <sup>125</sup>I seeds), there was a trend toward improved bNED rates with combined treatment compared with brachytherapy alone (Table 6). Ragde and colleagues<sup>22</sup> reported positive biopsy results in 27% of 108 patients in the combined treatment and the brachytherapy groups (at median 55 months), whereas Kaye and colleagues<sup>20</sup> found no difference in positive biopsy rates between the combined treatment group and the brachytherapy group (20% v. 17% respectively).

The most commonly reported adverse effects were grade 1 and 2 diarrhea and dysuria (in 88% of cases in the 3 studies). Grade 3 dysuria and diarrhea occurred in 3% of 33 patients. Rectal pain or tenesmus occurred in 55% of patients and persistent urinary retention in 21%. Other symptoms included urinary incontinence (in 9%), urinary tract infection (in 6%) and persistent perineal pain (in 12%). Chronic toxicity was not well described. In the one series reporting

potency,<sup>21</sup> 82% of the patients maintained potency at 1 year and 77% at 2 years.

### Brachytherapy preceding external beam radiotherapy

Critz and associates<sup>23</sup> reported experience with brachytherapy using <sup>125</sup>I seeds followed by external beam radiotherapy in 1020 men treated between 1984 and 1996. A retro-pubic freehand technique was used to guide implantation in the early years. Three weeks after implantation external beam radiotherapy (45 Gy in 30 fractions) was delivered to the prostate bed. Median follow-up was 2 years for patients whose implantation was guided by transrectal ultrasound. At 5 years, 92% were biochemically free of recurrence.

Although Critz and associates did not report biopsy data, Iversen and associates<sup>24</sup> did. They obtained annual biopsy specimens from 32 patients given a similar combination of brachytherapy plus external beam radiotherapy; the median follow-up was 35 months. Twelve (48%) of 25 patients had positive biopsy results.

Adverse effects were reported in one series.<sup>24</sup> Of the 32 patients 75% experienced mild and transient cystitis or diarrhea. Rectovesical fistula occurred in 6%, anal ulcer in 3%, hemorrhagic proctitis in 16% and severe persistent cystitis in 25%.

## Interpretation

The Memorial Sloan–Kettering Cancer Center experi-

**Table 6: Studies of brachytherapy as a boost to external beam radiotherapy**

Study	No. of evaluable cases	Tumour stage, group size	Gleason score, group size	Median follow-up, (and range), mo	Rate of freedom from failure, % (and no. of cases)
Dattoli et al <sup>21</sup> (case series)*	73	T2a: 2 T2b: 16 T2c: 19 T3: 36	4: 5 5–6: 28 7–9: 40	24 (12–36)	bNED (3-yr): 79
Kaye et al <sup>20</sup> (comparative cohort study)	Group 1: 45 (brachytherapy† only) Group 2: 31 (external beam radiation plus brachytherapy†)	T1: 2 T2: 43 T1: 3 T2: 28	< 7: 40 ≥ 7: 5 < 7: 20 ≥ 7: 11	26‡ (11–60)	cNED: Group 1: 51 (21/41) Group 2: 63 (19/30)
Ragde et al <sup>22</sup> (comparative cohort study)	Group 1: 98 (brachytherapy† only) Group 2: 54 (external beam radiation plus brachytherapy†)	T1a: 4 T1b: 10 T1c: 6 T2a: 56 T2b: 22 T1b: 2 T1c: 4 T2a: 20 T2b: 14 T2c: 10 T3a: 3	≤ 4: 44 5–6: 52 ≥ 7: 0 ≤ 4: 2 5–6: 39 ≥ 7: 13	119 (3–134)	bNED (10-yr): Group 1: 60 (58/96) Group 2: 76 (39/51)

Note: bNED = biochemically no evidence of disease, cNED = clinically no evidence of disease.

\*Brachytherapy with palladium 103 seeds.

†Brachytherapy with iodine 125 seeds.

‡Mean.

ence of the 1970s<sup>6</sup> did not meet the technical criteria for inclusion in this review. However, the local relapse-free rate of 21% at 15 years is sobering evidence of the continued risk of late local recurrence and the necessity of adequate follow-up. With the modern brachytherapy technique, transrectal ultrasound guidance has resulted in improved seed alignment and spacing, and improved implant homogeneity, whereas treatment-planning software has provided precision in pre-planning the implant and evaluating the final result.

Pretreatment prognostic factors such as tumour stage, Gleason score and serum PSA level influence the outcome of any definitive treatment of localized prostate cancer. Clinical experience indicates that permanent implantation of <sup>125</sup>I or <sup>103</sup>Pd seeds under transrectal ultrasound guidance yields promising short- and intermediate-term rates of freedom from biochemical failure among selected patients with early-stage prostate cancer. Results appear to be comparable among selected patients with T1c or T2a tumours, a Gleason score of 6 or lower and a serum PSA level of 10 µg/L or less. For less favourable tumours, the results of brachytherapy as monotherapy are inferior to other modalities. The addition of external beam radiotherapy may improve results by increasing the margin of coverage in the periprostatic tissue, but alternatives such as dose-escalated 3-dimensional conformal radiotherapy should be considered.

Patient selection is also important for technical reasons. Prior transurethral resection of the prostate is a relative contraindication because the surgical defect can interfere with optimal seed placement. Pubic arch interference can pose problems in implanting seeds in the anterolateral aspects of larger prostates. Therefore, prostate glands should ideally be less than 45–50 mL in size.

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. The spectrum of possible side effects after brachytherapy may be more acceptable to patients than that associated with external beam radiotherapy or radical prostatectomy. Issues such as quality of life, patient preference and cost are important considerations.

Results from randomized trials with adequate follow-up are key in the evaluation of new and emerging therapies such as brachytherapy. At present, there is insufficient evidence to unconditionally recommend the use of brachytherapy over current standard therapies. Whenever possible, patients should be asked to participate in randomized trials comparing brachytherapy and standard treatment with radical prostatectomy or external beam radiotherapy.

To minimize the risk of recurrence from subclinical extraprostatic disease,<sup>25</sup> brachytherapy should be offered only to selected patients with favourable disease (T1c or T2a tumour, Gleason score of 6 or lower and serum PSA level of 10 µg/L or less). Patients should be well informed about alternative therapies and potential adverse effects.

*Competing interests:* None declared.

*Contributors:* Dr. Crook was the principal investigator; she conducted the study and had primary responsibility for writing the manuscript. Drs. Lukka and Klotz contributed to the analysis of the results and provided advice during the preparation of the manuscript. Ms. Bestic and Ms. Johnston assisted with the literature search and the preparation of the manuscript.

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**Appendix 1: TNM classification system for prostate cancer<sup>26</sup>**

Stage	Definition
<b>T1</b>	Clinically inapparent tumour, neither palpable nor visible by imaging
T1a	Incidental finding in < 5% of tissue resected during TURP
T1b	Incidental finding in > 5% of tissue resected during TURP
T1c	Identified by needle biopsy because of elevated serum PSA level
<b>T2</b>	Tumour confined within the prostate
T2a	One lobe involved
T2b	Both lobes involved
<b>T3</b>	Tumour extends through prostate capsule
T3a	Unilateral or bilateral extracapsular extension
T3b	Seminal vesicles involved
<b>T4</b>	Fixed or invades adjacent structures

Note: TURP = transurethral resection of the prostate, PSA = prostate-specific antigen.