The Alberta Heritage Foundation
for Medical Research

Brachytherapy for prostate cancer

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Glossary

3D-CRT - three dimensional conformal radiotherapy

bNED - biochemically no evidence of disease

BT - brachytherapy

CSAP - cryosurgical ablation of prostate

CT - computed tomography

EBRT - external beam radiotherapy

iPSA - initial PSA level prior to treatment

PSA - prostate serum antigen

RP - radical prostatectomy

TRUS - transrectal ultrasound

Summary

- Brachytherapy is a radiotherapy technique that has been used to treat prostate cancer that is believed to be confined to the capsule. There has been increased interest in its use, following development of new techniques and improved diagnostic imaging methods.
- Alternative management techniques for prostate cancer include radical prostatectomy, external beam radiotherapy, hormone therapy and watchful waiting.
- Brachytherapy has potential advantages through being less invasive than radical prostatectomy and associated with lower morbidity.
- Establishing the efficacy of brachytherapy treatment is difficult given the long follow-ups that are required for a slowly developing disease such as prostate cancer, the lack of prospective randomized clinical trials, variation in study populations, and variation in procedures and processes undertaken.
- Biochemical outcomes indicate that brachytherapy is a reasonable option for treatment of early prostate cancer in the short term, or as a boost to external beam radiation in more advanced stages. Biochemical control rates range from 95% to as low as 60% with 10 year follow-up. This range reflects the diversity of patient populations being studied, as well as varying technique.
- Disease recurrence revealed through positive biopsies ranges from 5-35% and depends upon the study protocol and time of follow-up. The non-biochemical outcomes follow the same trends as biochemical outcomes. However the percentage recurrence is lower with biopsy, which underestimates local recurrence.
- Disease-specific deaths in series treated with brachytherapy range from 0-3%. Overall survival ranges from 65% for studies with long follow-up, to no reported deaths.
- Brachytherapy appears a promising intervention for localized prostate cancer in the short term. However, its potential for influencing overall outcomes, particularly long term morbidity and survival, are unknown. It is possible that there may be some bias in the existing reports towards selection of more promising candidates for treatment.
- Alternative or complementary treatments such as radical prostatectomy, external beam radiotherapy are continuing to evolve so that the safety and efficacy of brachytherapy relative to these is not certain and may continue to change.

- Given these uncertainties, which are likely to continue, the choice of treatment for localised prostate cancer will likely continue to be made on the basis of physician and patient preference, rather than as a result of scientific proof that one treatment modality is of superior effectiveness.
- In terms of health care in Alberta it is suggested that the status and outcomes from the technology be kept under review. Also, any use in the province of brachytherapy for prostate cancer should be linked to long term prospective collection of patient outcomes data.

Introduction

In November 1997, AHFMR published a short report on brachytherapy for treatment of prostate cancer (2). This was in response to a request for information from Alberta Health on the status of this technology. The present report has been prepared as a follow up to the previous assessment because of continued interest in the technology by the health ministry and others. It considers studies that have been reported in the literature since completion of the earlier assessment (1997-1999) and focuses on the efficacy and effectiveness of the technique.

Brachytherapy is an older radiotherapy technology that involves placement of radioisotope seeds in the prostate gland. There has been increased interest in its use, following development of new techniques and improved diagnostic imaging methods. The new imaging methods, including fluoroscopic guidance, computed tomography (CT), and transrectal ultrasound (TRUS), allow for accurate treatment planning and seed placement. In addition, post treatment imaging allows for routine analysis of the accuracy of seed placement, and continual improvement of technique. Use of experimental imaging methods such as those combining magnetic resonance imaging with should continue to increase the accuracy with which the seeds are placed in the prostate (10).

Various isotopes are used in brachytherapy, most commonly ^{125}I or ^{103}Pd. However, ^{192}Ir and ^{198}Au are also being used. Differences in energy, initial dose rate and half-life of these isotopes are, in principle, being exploited to best treat different types of tumours. A specific dose rate may be most effective against either less differentiated tumours, or at more advanced stages of disease. To date, however, the comparative performance of these isotopes in brachytherapy, in terms of their effect on patient outcomes, is not certain.

In addition, there are a number of techniques to administer brachytherapy, including permanent implants, or temporary implants at low or high dose rate. The method chosen will influence the choice of isotope, and each method has different equipment and space requirements. High-dose-rate temporary implants require a shielded room for the procedure, while low-dose-rate temporary implants require hospitalization and isolation of the patient. By comparison, permanent implants allow the patient to return home quickly. Brachytherapy can also be used in conjunction with other methods. For instance, it may be used as a boost to external beam radiotherapy (EBRT) in patients with more advanced disease.

The earlier AHFMR report concluded that the quality of evidence on effectiveness of brachytherapy as a treatment for prostate cancer was still comparatively limited, particularly for longer-term outcomes. However,

brachytherapy was increasingly regarded as a useful option for appropriately selected patients, both as monotherapy and in combination with EBRT.

Establishment of comparative effectiveness of techniques for treatment of prostate cancer is difficult due to the long follow-up required to determine outcomes. Also, the effectiveness of alternative technologies, particularly EBRT, continues to change so that care must be taken in comparing their performance with that of brachytherapy. Technology is improving in applying dose more specifically to cancerous tissue and avoiding surrounding tissue damage, while techniques in use for radical prostatectomy (RP) are increasingly sparing nerves and tissue surrounding the prostate and decreasing the incidence of incontinence and impotence.

Methodology used in the literature review for this report is given in Appendix A. A summary of studies considered in the earlier report has been included as Appendix B.

Clinical Outcomes

Results of the studies on the efficacy of brachytherapy are presented in abbreviated form in Table 1 and the data extraction sheets in Appendix C provide more detail. The results indicate that, in the short term, brachytherapy is an effective treatment in appropriately selected patients.

Table 1: Summary of clinical trials

Study	Subjects	Method	Outcome	Survival Outcome	Author's Conclusions
D'Amico et al., 1998 (11)	Retrospective n=1872 RP 888 Brachytherapy 218 EBRT 766 Stage: Low risk group: T1c, T2a, and PSA of 10ng/mL or less, and Gleason 6 or less Intermediate risk group: PSA levels higher than 10, less than 20 ng/mL, Gleason of 7, clinical stage T2b High risk group: T2c disease, or PSA level of more than 20 ng/mL, or a biopsy Gleason score of 8 or more	^{103} Pd Radical prostatectomy, Brachytherapy, or Conformal external beam radiotherapy Follow-up: RP 38 months (8-100) EBRT 38 months (8-75) Brachytherapy 41 months (3-72)	Relative Risk of PSA failure No significant difference noted between treatments for low risk patients. Intermediate risk patients did significantly worse with brachytherapy alone, but fared equivalently to RP if androgen deprivation also used. High risk patients treated with RP or EBRT did significantly better than those with brachytherapy +/- androgen deprivation.	No patients lost to follow-up or died	No statistical difference for 5 year PSA outcome between RP, EBRT, or brachytherapy treatment modalities in low risk patients with or without neoadjuvant androgen deprivation Intermediate and high-risk patients treated with RP or EBRT did better than those treated by brachytherapy. Brachytherapy for prostate cancer therapy may be clinically efficacious in a select subgroup of patients and possibly inadequate in others.
Zelefsky et al., 1999 (56)	Retrospective n=282 EBRT 137 Brachytherapy 145 Stage: Pretreatment PSA ≤10ng/mL, Gleason score ≤6 for EBRT and ≤7 for brachytherapy, clinical stage ≤T2b	^{125} I Brachytherapy or 3D conformal radiotherapy Both groups +/- neoadjuvant androgen deprivation therapy TRUS not used routinely, fluoroscopy is used. Follow-up: EBRT 36 months (12-109) Brachytherapy 24 months (6-103)	5 y. actuarial PSA relapse-free survival rates 88% for CRT and 82% for brachytherapy.	No information on survival. Presumably no deaths.	Both 3D-CRT and brachytherapy are associated with an excellent PSA outcome for patients with early-stage prostate cancer.

Table 1: Summary of clinical trials (cont'd)

Study	Subjects	Method	Outcome	Survival Outcome	Author's Conclusions
King et al. 1998 (22)	Retrospective n=221 RP 73 EBRT 85 Brachytherapy 63 Stage: PSA ≤20ng/mL, Gleason ≤8 Median Gleason 6 Median PSA Brachytherapy 7.9 EBRT 9.7 RP 8.9	^{103} Pd ^{125} I Radical prostatectomy, brachytherapy, or external beam radiotherapy Follow-up median: Brachytherapy 13 months EBRT 20 months RP 31 months	Biochemical disease-free survival (bNED) Actuarial bNED at 48 months: All patients: RP 69.9% IMP 60.3% EB 43.5% iPSA ≤10ng/mL RP 75.6% IMP 66.7% EB 51.0%	No comment on survival	There was no statistically significant difference between radical prostatectomy and brachytherapy. Outcomes from brachytherapy are similar to surgery and superior to EBRT in the first four years following treatment.
Koutrouvelis 1998 (24)	Retrospective Technique presentation more than clinical trial n=130 Stage: Clinical stage A,B, or C adenocarcinoma Gleason score 2-9 PSA range 0.9-143 ng/mL, mean 16.25	^{103} Pd ^{125} I Brachytherapy or Brachytherapy + hormone Follow-up: 6-24 months	95% of patients achieved a PSA ≤ 2ng/mL	No comment on survival	Initial clinical and biochemical results with this method are promising.

Table 1: Summary of clinical trials (cont'd)

Study	Subjects	Method	Outcome	Survival Outcome	Author's Conclusions
Sharkey et al. 1998 (38)	Retrospective n=434 Stage: Average PSA 7.5ng/mL (0.1-48.8ng/mL) 95% clinically stage 2 Gleason score 2-10 with 74%<7.	^{103} Pd Brachytherapy or Brachytherapy + hormone Follow-up: Mean 2.3 y (up to 5 y.)	bNED (PSA) at 4-y (n=81) Brachytherapy: 81% Brachytherapy + hormone: 79% Total patients: 80% bNED (PSA) 1-y (n=425) Brachytherapy: 76% Brachytherapy + hormone: 86% Total patients: 81% Negative biopsy at 2 years: Pd monotherapy: 90% Brachytherapy + hormone therapy: 89%	No disease related deaths.	Results are comparable to external-beam radiation therapy. It is associated with less morbidity than standard external-beam radiation therapy.
Storey et al. 1999 (44)	Prospective ? 193 Stage: T1 or T2 Gleason ≤7 PSA ≤10, 100 PSA >10, 83	^{125} I Brachytherapy Follow-up: Median 35 months	5 y actuarial biochemical freedom from failure rate 63% (failure defined as three consecutive rises in PSA) Five-year actuarial biochemical freedom from disease was 76% and 51% for patients with a pretreatment PSA ≤10ng/mL, >10ng/mL respectively. Disease free survival for patients with PSA ≤4ng/mL and >4≤10ng/mL was 84% and 72% respectively.	Five year actuarial survival 66%	Brachytherapy is efficacious and feasible for certain populations of elderly patients with favourable prognostic indicators, while patients with poor prognostic indicators do no appear to be candidates for brachytherapy alone. Proper patient selection is necessary to obtain results comparable to EBRT and radical prostatectomy.

Table 1: Summary of clinical trials (cont'd)

Study	Subjects	Method	Outcome	Survival Outcome	Author's Conclusions
Ragde et al. 1997 (34)	Prospective n=122 Stage: T1 23% T2 77% PSA $\leq$ 4 44% PSA >4-10 34% PSA >10 22%	^{125}I Brachytherapy Follow-up: Median 69.3 months	7-y Actuarial disease free survival 79% (PSA >0.5ng/mL)	Overall 7 y. survival was 77%. 4 men died within 1 year post brachytherapy of intercurrent illness, and were excluded from the study. No deaths from prostate cancer in this cohort.	7-year outcomes are excellent and competitive with radical prostatectomy. These, combined with single-session, outpatient nature of procedure, high patient acceptance, and minimal morbidity, should encourage further evaluation of brachytherapy for early stage prostate cancer.
Ramos et al. 1999 (36)	Retrospective Computer randomly selected clinically matched patients n=299 Stage: Matched for preoperative Gleason score, PSA, and clinical stage to Ragde *et al.*, 1997 study Gleason 2-6 PSA<4, 4.1-9.9, 1-0-40 ng/mL Clinical Stage T1, T2a, T2b, T2c	Radical prostatectomy Comparison to Ragde *et al.*, 1997 brachytherapy Follow-up: Mean 60 +/- 35 months	7-y probability of non progression 84%. This compares to 79% in Ragde *et al.*, 1997 series. 31/299 had PSA recurrence only 4/99 had recurrence locally, distant, or both. Thus overall failure rate 11% or 35/299.	No comment on survival	Radical prostatectomy yielded a proportionately but not statistically significant higher 7-year probability of non-progression than ^{125}I brachytherapy in patients with favourable clinicopathological characteristics. Comparisons are confounded by residual differences in clinicopathological features of tumors between groups and different treatment end points to determine outcomes.

Table 1: Summary of clinical trials (cont'd)

Study	Subjects	Method	Outcome	Survival Outcome	Author's Conclusions
Polascik et al. 1998 (32)	Retrospective n=76 Stage: Matched for Gleason score and clinical stage to Ragde *et al.*, 1997 Gleason score 2-6 Clinically localized (T1, T2)	Radical prostatectomy Results are compared to Ragde *et al.*, 1997 brachytherapy. Follow-up: Mean 83.2 +/- 22.8 months (12-108)	7 y. Actuarial PSA progression-free survival 97.8% This compares to 79% bNED in Ragde *et al.*, 1997 series	No deaths due to prostate cancer.	Failure rates may be higher following ^{125}I brachytherapy compared to radical prostatectomy. The results emphasize the need for caution in interpreting the relative efficacy of brachytherapy in controlling localized prostate cancer.
Ragde et al. 1998 (35))	Prospective n=147 Stage: T1-T3 PSA 0.4-138 ng/mL, average 11.0 ng/mL Gleason median 5 (2-10)	^{125} I Brachytherapy or Brachytherapy +EBRT Follow-up: Median 119 months (3-134)	10-y disease free (PSA) survival: brachytherapy alone: 60% brachytherapy +EBRT: 76% combined: 66% 23 (15%) of patients had positive biopsies. 29% of patients did not have a biopsy, thus 22.3% of those that had a biopsy were positive.	At last follow-up 3/153 (2%) patients died of prostate cancer Disease specific survival: 98% Five patients lost to follow-up. 53 patients died during the 10-y study. 65% overall survival. 30/53 died with NED, 20 with recurrent disease died of other causes.	Brachytherapy is a valid and efficient option for treating patients with clinically organ-confined, low to high Gleason grade, prostate carcinoma. 10-year follow-up demonstrates PSA levels superior to those reported in several published EBRT series, and comparable to those published in a number of radical prostatectomy series.

Table 1: Summary of clinical trials (cont'd)

Study	Subjects	Method	Outcome	Survival Outcome	Author's Conclusions
Stokes et al. 1997 (41)	Retrospective n=142 Stage: Organ confined adenocarcinoma of the prostate Gleason score ≤7 Well to moderately well differentiated tumour Tumour clinically confined to the prostate PSA≤50ng/mL, mean 10.6ng/mL	^{125}I Brachytherapy Follow-up: Median 30 months (1-6 years)	16.9% - (24/142) patients have recurrent or persistent cancer. 2.8% (4) have local prostate recurrence confirmed by biopsy. 2.8%(4) have metastatic bone disease 11% (16) have an increasing PSA without demonstrable clinical tumor, negative prostate biopsy, and scans, and are considered to have occult systemic metastasis. Overall disease free survival at 2 years is 90%, and at 5 years is 76%.	2.8% (4) of patients died of metastatic cancer	The study found 97% local control in the prostate and 76% NED survival and author's comment that this is comparable to EBRT without the lengthy course of outpatient radiation therapy. Brachytherapy is an attractive alternative for early carcinoma of the prostate.
Nori and Moni 1997 (30)	Retrospective n=47 Stage: T2a Median iPSA 11.3ng/mL (1.5-100)	^{103}Pd ^{125}I Brachytherapy Follow-up: median 37 months	Local recurrence in 5/46 patients (11%) Isolated biochemical failure in 8/46 (17%) Actuarial clinical freedom-from-relapse was 79% at 5 years Actuarial biochemical freedom from relapse 64% at 5 years	No comment on survival	Authors recommend brachytherapy for good risk patients, and a combination of EBRT and brachytherapy for intermediate risk group.

Table 1: Summary of clinical trials (cont'd)

Study	Subjects	Method	Outcome	Survival Outcome	Author's Conclusions
Grado et al. 1998 (16)	Retrospective n=490 Stage: PSA median 7.5ng/mL (0.1-117.2)T1-T3c Tumour well differentiated 23% Moderately differentiated 54% Poorly differentiated 23%	^{103} Pd ^{125} I Brachytherapy or Brachytherapy +EBRT Follow-up: Median 46.9 months (22.1-94.6)	Actuarial disease free survival at 5 y was 79%. Disease free in terms of PSA, biopsy, bone scan, CT scan or DRE. Local treatment failure in 5/490 Regional failure in 3/490 Distant failure in 33/490 Failure of unknown origin in 5/490 3/490 patients experienced both local and distant failure	No comment on overall survival	A broad range of patients with localized prostate cancer can benefit from brachytherapy with minimal morbidity.
Stone and Stock 1999 (43)	Prospective ? n=301 109 low risk 152 moderate risk 40 high risk Stage Low risk: T2a or less, Gleason 6 or less, PSA 10ng/mL or less. Moderate risk: T2b – T2c, Gleason 7 or greater, PSA greater than 10 ng/mL. High risk: T2c-T3c, Gleason 8 or greater, PSA greater than 15ng/mL.	^{103} Pd ^{125} I Low risk: brachytherapy Moderate risk: brachytherapy +/- 5 months of hormonal therapy high risk: brachytherapy + EBRT + 9 months of hormonal therapy. Follow-up: Low risk: 18 months (1-7 years) Moderate risk: 27 months (12-74) High risk: 13 months (6-42 months)	Low risk: 4-y freedom from PSA failure rate was 91%. Moderate risk: 4-y biochemical freedom from failure rate for the hormone group was 85% versus 58% for the no hormone group High risk: the 3-y biochemical freedom from failure rate was 71%. Prostate biopsies negative in 87% of low risk, 96.8 (hormone) and 68.6% (non hormone) of the moderate group, and 86% of high risk patients.	N/A	Outcomes in low risk patients treated with ^{125}I alone compare favorably to what has been reported for similar groups of patients treated with radical prostatectomy or EBRT. Intermediate risk patients demonstrate inferior results compared to patients with low risk patients. Brachytherapy can be accomplished with low morbidity.

Table 1: Summary of clinical trials (cont'd)

Study	Subjects	Method	Outcome	Survival Outcome	Author's Conclusions
Critz et al. 1998 (8)	Retrospective n=1020 Stage: Median PSA 7.5 ng/mL (0.2-188) T1T2N0 Well differentiated 27% Moderately differentiated 54% Poorly differentiated 19%	^{125}I Brachytherapy +EBRT Follow-up: 3 years (1-14 years)	Actuarial overall 5 y. disease free (PSA) survival 79% Actuarial overall 10 y. disease free (PSA) survival 72%	No comment on overall survival	The 10-year disease-free survival results of simultaneous radiation, are comparable to those in reports after radical prostatectomy.
Zeitlin et al. 1998 (54))	Single Institution treatment program n=212 Stage: T1-T3	^{103} Pd ^{125} I Brachytherapy +EBRT Follow-up: Mean 33 months (24-60)	Disease-free survivor rate (PSA) at 5 y. was 72% when iPSA >20ng/mL, vs. 95% when iPSA ≤20ng/mL. Positive biopsies in 13.9% (20/144)	3 non prostate cancer deaths, no mention of deaths from prostate cancer.	The short-term results of high dose combination radiotherapy for localized prostate cancer are promising.
Mate et al. 1998 (28)	Pilot study n=103 Stage: Mean PSA 12.9ng/mL with 90% of patients above 4.0	^{192}Ir Brachytherapy + EBRT Follow-up: 45 months (10-89)	Actuarial 5 y progression free survival 84% for iPSA<20ng/mL 50% for iPSA>20ng/mL 14.6% of patients experienced biochemical failure.	No mention of overall survival.	HDR-Ir^{192} , followed by moderate-dose external-beam radiotherapy is a well tolerated and effective treatment for localized prostate cancer.
Dinges et al. 1998 (13)	Prospective n=82 Stage: PSA value ≥10ng/mL in 64.6% patients. Median PSA 14.0 ng/mL	^{192}Ir Brachytherapy + EBRT Follow-up: 24 months	PSA <1.0 ng/mL in 52.9% of patients at 2 y. Negative biopsies 24 months after therapy in 73.1% of patients.	3 patients lost during follow-up. No comment on overall survival.	Combined brachytherapy and EBRT is feasible and well tolerable. The rate of negative prostate biopsies represents an encouraging result. The follow-up time is too short, however, to comment upon the efficacy.

Table 1: Summary of clinical trials (cont'd)

Study	Subjects	Method	Outcome	Survival Outcome	Author's Conclusions
Stromberg et al. 1997 (46)	Retrospective n=58: EBRT with brachytherapy boost n=278: EBRT Median pretreatment PSA for EBRT 14.3ng/mL, Gleason 6, T2b to T3c EBRT + brachytherapy boost: 14.0ng/mL, Gleason 7, T2b to T3c All patients without evidence of nodal or distant metastases	^{192}Ir Brachytherapy + EBRT Follow-up: EBRT 43 months (1-91) EBRT + brachytherapy boost 26 months (3-51)	3 year actuarial biochemical control rates were 85% versus 52% for the conformally and conventionally treated patients, respectively.	No comment on survival	Results show a significant improvement in the biochemical response rate with conformal boost brachytherapy and pelvic external radiation compared with conventional EBRT alone.
Borghede et al. 1997 (6)	Retrospective n=50 38 patients with stage T1-2 12 patients with stage T3 30patients PSA <10ng/mL 12 10-20ng/mL 8 > 20ng/mL	^{192}Ir Brachytherapy + EBRT Follow-up: 45 months (18-92)	Clinical and biopsy verified local control achieved in 48/50 (96%) patients. Post-treatment PSA $\leq$1.0ng/mL was seen in 42 (84%) patients	No patient has succumbed due to the prostatic carcinoma. Two of the patients died during the follow-up of concurrent illness with prostate.	Local control results and minimal toxicity are promising. Long term results are necessary before general use.
Paul et al. 1997 (31)	Retrospective n=40 Pretreatment PSA mean 40.7 ng/mL, median 11.3ng/mL(0.5-406ng/mL) 5 T1 tumours, 18 T2, and 17 T3	^{192}Ir Brachytherapy + EBRT Follow-up: Mean 74 months (16-130)	Of 35 surviving patients, 7 suffered from clinical progression of disease (20.5%). 4 of these 7 patients had a positive biopsy 18 months after treatment. 32/40 patients had biopsies at 18 months, 21 showed no evidence of disease, 11 (34%) had a positive biopsy.	35/40 patients remain alive. 4 patients died of other illness, and one from prostate cancer.	Results compare favourably with the rates of disease-free survival observed at 5 years, which range from 40-90% following different techniques of radiotherapy for localized prostate cancer as reported in the literature. The rate of positive biopsy increases with higher tumour stage at diagnosis, therefore tumour control obtained in locally advanced disease by this method is insufficient.

Table 1: Summary of clinical trials (cont'd)

Study	Subjects	Method	Biochemical Outcome	Survival Outcome	Author's Conclusions
Teh et al. 1998 (47)	Retrospective Stage: Localy recurrent prostate cancer after failing initial combined brachytherapy + EBRT	^{198}Au Salvage brachytherapy Follow-up: 54 months (12-79)	5/30 patients showed control of disease progression. 25 patients had rising PSA on at least 3 consecutive measurements	No comment on survival.	Brachytherapy with permanent ^{198}Au seeds is a feasible option in a selected group of patients with locally recurrent prostate cancer and a low level of PSA. Re-implant with 198Au seeds can be performed with acceptable morbidity.
Grado et al. 1999 (15)	Retrospective n=49 Stage: PSA median 5.6 ng/mL (1.5-79.1) 46 had EBRT previously 3 had brachytherapy previously median elapsed time between primary therapy and salvage therapy was 41.7 months (21.8-185.2) well differentiated 10% moderately differentiated 35% poorly differentiated 55%	^{125} I ^{103} Pd Salvage Brachytherapy +/- EBRT +/- neoadjuvant hormone therapy Follow-up median 64.1 months (26.6-96.8)	Actuarial biochemical disease free survival at 3 and 5-y 48% and 34% respectively. Local failure 1 patient Distant failure in 26	Disease specific survival at 3 and 5 years was 89% and 79 % respectively. Overall survival at 3 and 5 years was 75% and 56 % respectively. It is low due to the significant co-morbidities in this group.	Brachytherapy is a potentially curative salvage treatment for patients in whom prior radiotherapy failed. Given the poor prognosis of these patients, this modality was associated with a high rate of local control.

Biochemical control as a measure of prostate cancer recurrence

The majority of studies reported their results in whole or in part in terms of biochemical control, that is the level of prostate serum antigen (PSA) in the patient's blood. A limitation of this method is that there is inconclusive evidence on how long it is appropriate to wait for the PSA level to reach a nadir following radiotherapy. There is also uncertainty as to level of PSA present in serum that represents an absence of cancerous prostate tissue. It is a comparatively easy test to perform for follow-up and yields early indications of disease recurrence.

The biochemical results reported in the reviewed papers appear good in the short term. There is a lack of comparison with other treatment modalities. In addition, all of the studies would be more useful if they had included a subset of patients who underwent watchful waiting in order to determine if brachytherapy was an effective cure, or if the results simply reflect the slow progress of the disease. Brief details of the results obtained are as follows.

Studies that compare **different treatment modalities** include:

- D'Amico et al. (11) found no statistical difference for a five year PSA outcome between RP, EBRT and brachytherapy in low risk patients. Intermediate and high risk patients did better with RP or EBRT than with brachytherapy.
- Zelefsky et al. (56) found conformal radiotherapy (CRT) had slightly higher five year relapse free rate than brachytherapy (88% vs. 82%).
- King et al. (22) compared RP, brachytherapy and EBRT. They found that at four years there was no statistically significant difference between RP and brachytherapy, but that EBRT was associated with poorer outcomes.

The results of studies on **brachytherapy without comparison to other treatment modalities** demonstrated:

- 95% success at 6 - 24 months follow-up (Koutrouvelis), 80% success in patients followed for four years (Sharkey et al.), 63% actuarial freedom from disease at five years (Storey et al.), 79% success seven-year actuarial outcome (Ragde et al. 1997), a four year actuarial success for low risk patients of 91% (Stone and Stock), an actuarial five year disease free survival of 76% (Stokes et al.) and an actuarial biochemical freedom from relapse of 64% at five years (Nori & Moni).

Two **retrospective studies of surgery** compared their results to the brachytherapy results of Ragde et al. (35):

- Ramos et al. (36) reported a seven year actuarial probability of non-progression of 84% following RP, while Polascik et al. (32) had a seven year actuarial rate of 97.8% for their series. As a result, in these two cases RP

marginally outperformed brachytherapy, on the basis of results reported from an unrelated study at another centre.

Two studies report on both **brachytherapy, and brachytherapy plus EBRT:**

- In a study with 10-year follow-up Ragde et al. (35) the actuarial freedom from disease was 60%. In an editorial comment on this study it is noted that this is far down from the actuarial result of 79% at seven years reported for an overlapping cohort of patients (52). Furthermore, brachytherapy + EBRT had an actuarial success rate of 76% at 10 years, despite the fact that the patients who were treated this way were initially considered to be at higher risk. This suggests that adding EBRT provides a significant improvement in outcomes over brachytherapy alone. These long-term outcomes suggest that short-term results may be misleading, and that brachytherapy alone is not efficient for curative treatment of prostate cancer.
- The study by Grado et al. (16) did not differentiate between brachytherapy alone and brachytherapy + EBRT. They reported a five year actuarial result of 79%.

Other studies looked at the **effectiveness of brachytherapy plus EBRT alone**. These include:

- Stone & Stock (43) showing a three year actuarial success of 71% for high risk patients; Critz et al. (8) a five year actuarial success of 79%; Zeitlin et al. (54) a five year success of 95% for low risk patients, 72% for higher risk patients; Mate et al. (28) a five year actuarial success of 84% for low risk patients, 50% for higher risk patients; Dinges et al. (13) a 52.9% success at two years; Stromberg et al. (46) a three year actuarial success of 85% vs. 52% for EBRT alone; and Borghede et al. (6) 84% success at a mean of 45 months follow-up.

Finally, one study reported on biochemical control of patients using brachytherapy to treat recurring prostate cancer. In this Teh et al. (47) found that following use of brachytherapy for salvage treatment of prostate cancer, 83% of patients experienced biochemical failure.

Clinical control as a measure of prostate cancer recurrence

In addition to reporting biochemical evidence of disease status, various studies also utilized digital rectal exams (DRE), biopsy, bone scans and CT scans to diagnose recurrence of disease. The following studies reported these results.

Studies which report on **brachytherapy alone**:

- Sharkey et al. (38) report ~90% negative biopsy (10% positive), compared to biochemical results of 80%.
- Nori & Moni (30) report local recurrence in 11% of patients, compared to 17% that experienced biochemical failure.

- Stokes et al. (41) found 5% of patients had local recurrence confirmed by biopsy, or metastatic bone disease, compared to 16.9% failure detected biochemically.

Retrospective study on **radical prostatectomy which compares results to those of Ragde et al. on brachytherapy** (34):

- In the study of Ramos et al. (36) following RP, 4/299 (1.3%) experienced disease recurrence locally, distant, or both, identified from biopsy, while 31/299 (10.4%) had PSA recurrence alone.

Studies which look at **brachytherapy alone, or brachytherapy plus EBRT**:

- In the series described by Ragde et al. (35) 1998, 15% of total study population had positive biopsy, 29% of study group did not get a biopsy. Thus, for 22.3% of patients who had a biopsy, results were positive. This compares to 34% with biochemical failure.
- Grado et al. (16)1998 traced biochemical failure in 44/490 (8.9%) patients from biopsy, DRE, CT scans or bone scans and were unable to determine the source of biochemical failure in 5/490 (1%) patients. They give an actuarial five year failure rate of 21%.
- Stone and Stock (43), found that prostate biopsies were negative in 87% of low risk, 96.8 (hormone) and 68.6% (non hormone) of the moderate group, and 86% of high risk patients. This compares to 91, 85, 58, and 71% for bNED respectively.

Studies which looked at **brachytherapy plus EBRT**:

- Zeitlin et al. (54) found positive biopsies in 13.9% of those biopsied. This compares to an actuarial disease free survival of 72% by PSA. This paper reports positive biopsies in patients without biochemical failure.
- Dinges et al. (13) found 73.1% of biopsies were negative at 24 months post therapy, which compares to 52.9% biochemical control.
- Borghede et al. (6) found 96% negative biopsies at 18 months, compared to 84% biochemical control.
- Paul et al. (31) found 34% of those biopsied at 18 months were positive. No numbers are given for biochemical control.

In the study on brachytherapy for **treatment of recurrent prostate cancer** Grado et al. (15) found 27/49 (55%) cases of failure by DRE, biopsy, bone scan or CT scan. This compares to an actuarial bNED at 3 years of 48%.

Thus, the non-PSA results mirror the trends of the PSA outcomes but are less sensitive in detecting recurrence. This may be due to rising PSA levels predating the detection of cancer recurrence by other methods. Alternative possibilities are

that biopsy is not sensitive enough to detect the early stages of recurrence, or that PSA testing is producing false negatives. However, given the short follow-up times in most of these studies, PSA appears to be the best indicator of disease-free status in these studies. The study of Zeitlin et al. (54) demonstrated positive biopsies without biochemical failure, underlining the utility of following patients by more than one follow-up marker.

Overall survival

Studies may report either all deaths that occur of study participants, or deaths from prostate cancer. Due to the relatively short follow-ups in these studies, most report no deaths, or no deaths from prostate cancer. Several reports make no comment on survival. Of those that do:

- Sharkey et al. (38) and Polascik et al. (32), report no disease-related deaths;
- Storey et al. (44) report five year actuarial survival of 66%;
- Ragde et al. (34) report overall seven year survival of 77% with no deaths from prostate cancer;
- Ragde et al. (35) report 3/153 (2%) of patients died of prostate cancer, giving a disease specific survival of 98%, 65% overall survival during their 10 year study;
- Zeitlin et al. (54) report 3/212 non-prostate cancer related deaths;
- Borghede et al. (6) report 2/50 patients died during follow-up, none of prostate cancer;
- Paul et al. (31) found 1/40 patients died of prostate carcinoma, 4 died of other causes;
- Grado et al. (15), report disease specific survival at three and five years - 89 and 79% respectively; overall survival at three and five years was 75 and 56% respectively;
- Stokes et al. (41) report 2.8% (4/142) deaths due to metastatic disease with follow-up of one to six years.

Thus, the deaths from prostate cancer are in the 2-3% range, with the results reported by Grado et al. (15) being significantly higher as it is dealing with recurrent disease.

Little information on survival is available because disease progression is so long term. Overall survival in the reports reviewed here tend to be lower than disease-specific survival because of the age of the patient populations and significant co-morbidities. This means it is uncommon for the investigators to report deaths due to prostate cancer; usually deaths are from concomitant illness. In addition, brachytherapy would not be used on patients with advanced

disease, since it is a local treatment, and would not be appropriate to treat spread of the tumour beyond the prostatic capsule.

Complications

The complications reported for brachytherapy are detailed in Table 2. They include mild acute urethritis and proctitis for most patients. Long term complications seem restricted to a low percentage of the patient population and are similar to or lower than observed with EBRT or RP. Not all studies report complications, and few comment on impotence. Further, there is limited comparison of complications across the various treatment modalities, therefore it is difficult to choose a treatment based upon this information.

Only the retrospective study by Zelefsky et al. (56) directly compared two treatment modalities. This study reported slightly less long term urinary toxicity for CRT (8% grade 2, 1% grade 3) than for brachytherapy (31 % grade 2, 7% grade 3), similar GI toxicity (6% with CRT, 4% with brachytherapy) and higher levels of impotence with CRT (32% compared to 21% with brachytherapy). The authors comment that higher radiation dose seems to be a risk factor for impotence.

In the other studies, where incontinence is reported, it is usually 6% or less through all treatment modalities. The range for impotence is 5-38%, the greatest being in the study with brachytherapy + EBRT by Zeitlin et al. (54). Brachytherapy +/- EBRT showed a range of 5, 11.9, 15, 21 to 23.5% impotence in patients. Most long term GI morbidity seen in less than 5% of patients through all treatment modalities.

In conclusion, brachytherapy results in equivalent or fewer side effects than either EBRT or RP. As the technique evolves, seed placement planning is being further developed to reduce radiation to the surrounding tissue, while still providing an adequate dose to the tumour. Thus, complications can be expected to continue to decrease as the technique evolves. The complication rates of EBRT and RP are also expected to continue to decline.

Quality of Evidence

Assessing the effectiveness of brachytherapy for prostate cancer is difficult due to the absence of controlled trials, incomplete reporting of results, limited comparison with other treatment modalities, inadequate outcomes data for these other methods, and differences in patient populations.

The number of studies that directly compare brachytherapy to other modalities of treatment is very small, making the choice of best treatment difficult to discern from the available information. Studies focus upon the curative potential of brachytherapy, not how well it works in comparison to other treatments. A further complication of the long follow-up periods required to evaluate the effectiveness of brachytherapy is that the competing technologies such EBRT and RP continue to evolve. The presumption is that use of the newer versions of these technologies is resulting in improved therapeutic results and fewer complications. However, outcomes data for these more recent approaches are very limited. In some publications, brachytherapy is compared with earlier versions of technology, which are no longer state of the art.

Outcome measures vary between studies, making comparisons between different studies difficult. Differences in results might be due to the differing endpoints, or to the way the technique was carried out.

Many of the studies reviewed here conclude that brachytherapy may be a suitable treatment for patients in the early stages of prostate cancer. Thus, the follow-up time to determine success compared to other treatment modalities is 10-15 years, as this is a disease that progresses slowly in most individuals. Thus, the short follow-ups often reported are inadequate to determine if treatment has truly eradicated the cancer. Selecting for low risk patients, having no control group of watchful waiting or other treatment modalities, and allowing patient/physician preference for treatment, all influence patient distribution.

Additionally, comparative information on safety of the different modalities is scarce. Incomplete reporting, particularly with reference to complications but also on overall survival, makes comparisons difficult.

Published quality of life studies on brachytherapy generally report favourable results following treatment. However, they address only changes in life following brachytherapy or brachytherapy + EBRT and do not compare treatment modalities, making them of little use for comparative evaluations (4).

The methodological quality of the studies on brachytherapy, in terms of the classification of Jovell and Navarro-Rubio (19), is 'Poor' or 'Poor to Fair'. In that classification ‘Good’ refers to evidence from meta-analysis of randomised controlled trials (RCTs) or from large sample RCTs; ‘Good to Fair’ to that from small sample RCTs and non-randomised controlled prospective trials; ‘Fair’ to

results from non-randomised controlled retrospective trials, cohort studies and case-control studies; and 'Poor' to information from non-controlled clinical series and various other approaches. Assignment to categories is also dependent on conditions of scientific rigour.

There is fair evidence for short-term biochemical survival but poor evidence for effects of the treatment on overall survival and for complications.

Discussion

The initial AHFMR report on this topic concluded that brachytherapy was a promising treatment for localized prostate cancer, but that evidence of efficacy was limited and that its place in health care was not well established.

The further review undertaken for the present report has confirmed this position. Additional useful information has emerged but the methodological quality of studies remains limited and there are still few data on longer-term outcomes.

The absence of controlled studies, and the variation in patient populations and in procedures and processes undertaken, present particular problems in assessing this technology. Undertaking the long term randomized clinical trials that would be necessary to definitively establish the efficacy of brachytherapy for prostate cancer would represent a considerable challenge for assessors. The American College of Surgeons Clinical Trials Group, in collaboration with the National Cancer Institute of Canada Clinical Trials Group, is planning a large study comparing brachytherapy and radical prostatectomy (Warde, personal communication). Patient accrual will occur over the next year. However, it will be 5 to 10 years before meaningful outcomes data will emerge. In the meantime, decisions on the technology will have to be made on the basis of results from weaker study designs and from incomplete and inconsistent data.

The present report confirms that brachytherapy appears a promising intervention in the short term. However, its potential for influencing overall outcomes, particularly long term morbidity and survival, are unknown. Patient selection issues discussed in the report make the prediction of its eventual effectiveness problematical. It is possible that there may be some bias in the existing reports towards selection of more promising candidates for treatment.

While brachytherapy shows promise, it needs to be borne in mind that alternative or complementary treatments such as EBRT and RP are continuing to evolve so that the safety and efficacy of brachytherapy relative to these is not certain and may continue to change.

These various uncertainties - which are unlikely to be resolved in the foreseeable future - pose difficulties for policy makers, health care professionals and their patients. The choice of treatment will likely continue to be made on the basis of physician and patient preference, rather than as a result of scientific proof that

one treatment modality is of superior effectiveness. In terms of health care in Alberta it is suggested that the status and outcomes from the technology be kept under review. Also, any use in the province of brachytherapy for prostate cancer should be linked to long term prospective collection of patient outcomes data.

Table 2: Complications of brachytherapy

Study	Complications
Zelefsky et al., 1999 (56)) CRT n=137 Brachytherapy n=145	• 3D-CRT 58% had no or only mild (grade 1) acute gastrourinary toxicity 42% grade 2 urinary symptoms requiring medication 91% had minimal to no late GU toxicity 8% had late grade 2 urinary symptoms 1% late grade 3 urinary toxicity (urethral stricture) 86% had no or mild (grade 1) acute gastrointestinal toxicity 14% had grade 2 requiring medication 94% minimal to no late rectal toxicity 6% had late grade 2 GI toxicity (rectal bleeding) Among patients who were potent before treatment 32% become impotent (32 /101) • Brachytherapy 3% had acute urinary retention (grade 3) no grade 4 urinary toxicity observed in either group. 62% had minimal to no late GU toxicity 31% grade 2 urinary toxicity that persisted more than 1 y. 7% late grade 3 urinary toxicity (urethral stricture) no late grade 4 urinary toxicity observed in either group No acute rectal symptoms 96% had minimal to no late rectal toxicity 4% experienced late grade 2 GI toxicity (rectal bleeding). Among patients who were potent before treatment 21% became impotent following therapy (28/132)
King et al., 1998 (22) BT n=63 RP n=73 EBRT n=85	• Brachytherapy minor urinary tract morbidity common Occasional rectal morbidity, non grade 3 or higher No TURP required or urinary incontinence • EB or RP No comments
Koutrouvelis 1998 (24) n=130	• Brachytherapy No hematoma or infection following procedure No incontinence complications 12% had radiation urethritis, cystits and / or proctitis, lasted for less than 1 month 6% had grade 2 complications for 1-4 months required alpha blockers no evidence of rectal ulceration or fistula 95% maintained ability for erection
Sharkey et al., 1998 ((38) n=434	• Brachytherapy Most patients had some degree of short-term bladder and bowel irritation, which required only symptomatic treatment. 5% experienced Incontinence, and only in those with previous TURP 15% experienced Impotence

Table 2: Complications of brachytherapy (cont'd)

Study	Complications
Storey et al., 1999 (44)) n=193	• Brachytherapy Occasional transitory urinary obstructive symptoms 5 / 193 patients required long term use of catheter up to 4 months 3 patients reported incontinence 18 reported minor post-brachytherapy dribbling 5 patients persistent hematuria for up to 6 weeks 2 patients developed rectal ulcers 8-10 months following brachytherapy one patient underwent radical prostatectomy with partial colectomy for prostatic necrosis
Ragde et al., 1997 ((34) n=122	• Brachytherapy Most patients experienced some degree of urinary urgency, frequency, and varying degrees of outlet obstruction, which usually subsided within a 5 to 10 month period. Temporary rectal symptoms rarely encountered. Late complications consisted mainly of urinary incontinence and urethral strictures. Of 118 patients followed for a median of 69.3 months post-brachytherapy, 112 patients remained continent of urine, and 6 patients became incontinent. Incontinence was limited to patients who had undergone a TURP. Thus an overall incontinence rate of 5.1% was observed. Five urinary diversions performed. Bulbomembranous urethral strictures occurred in 14/118 patients (12%).
Stokes et al., 1997 (41) n=142	• Brachytherapy Transient radiation urethritis several weeks following procedure, typical Grade 2 morbidity 19% ≥grade 3 4% - these numbers are after reducing dose to the periurethral area. one patient experienced a fatal pulmonary embolus 2 weeks post-implant, which may have been unrelated to his implant. 1 patient required a diverting colostomy to alleviate painful proctitis.
Nori and Moni, 1997 (30) n=47	• Brachytherapy Grade 3 urinary complications in 2/46 (4%) No grade 4 urinary complications No grade 3 or 4 rectal complications Erectile function preserved in 32 (86%) of the 37 patients who were sexually active prior to treatment.
Stone and Stock, 1999 (43) n=301 BT n=109 BT+ hormone n=152 BT + EBRT n=40	Brachytherapy Low risk: no patients experienced urinary incontinence. 4.5% of men experienced grade 1-2 radiation proctitis, and there were no cases of grade 3-4 radiation proctitis. Moderate risk: Grade 1 to 2 radiation proctitis occurred in 1 patient receiving hormonal therapy (1.3%) and in 3 treated only with brachytherapy (4%). There were no cases of grade 3 or 4 radiation proctitis No cases of urinary incontinence. Brachytherapy + EBRT High risk: All 5 patients who received 5920 cGy external beam dose had gastrointestinal complications. No grade 3 or 4 gastrointestinal complications. Actuarial freedom from grade 2 proctitis was 82%. No patient experienced urinary incontinence.
Grado et al., 1998 (16) n=490	• Brachytherapy +/- EBRT Acute urinary symptoms such as frequency, urgency, and nocturia common during the first 3 mo. following brachytherapy. 5 / 490 patients (1%) developed rectal fistula gross hematuria observed in 2 (0.4%) of patients significant post treatment pain in the form of penile dysuria in 4 (0.8%) and proctitis in 2 (0.4%)

Table 2: Complications of brachytherapy (cont'd)

Study	Complications
Zeitlin et al., 1998 ((54) n=212	• Brachytherapy + EBRT Proctitis in 21.4% Impotence in 38% of 100 patients potent before treatment Urinary retention in 1.5% Incontinence in 2.8% Rectoprostate fistula in 2.4% Rectal wall breakdown in 0.5% Urethral stricture in 0.5% 6 patients (2.8%) required colostomy and urinary diversion
Mate et al., 1998 (28) n=103	• Brachytherapy + EBRT No significant operative or perioperative complications were encountered. Genitourinary: 7: minor urethral stricure, 2: marked uropathy, 1: hematuria Gastrointestinal: 2: spotty rectal bleeding
Dinges et al., 1998 (13) n=82	• Brachytherapy + EBRT Acute side effects not increased over EBRT alone. Severe side effects were seen in 3 patients, rectourethral fistulae requiring colostomy
Borghede et al., 1997 (6) n=50	Brachytherapy + EBRT No serious bleeding or infections. Acute: 4 patients had mild to moderate dysuria 4 patients had urinary frequency no incontinence 40 patients had diarrhoea (5 mild, 35 moderate) Late side effects: 2 had mild dysuria 1 had mild haematuria 3 had urinary frequency 13 had mild diarrhoea 4 had moderate diarrhoea 1 had mild proctitis 5 had erectile dysfunction of 42 potent before treatment (11.9%)
Paul et al., 1997 (31) n=40	• Brachytherapy + EBRT • Of the 17 patients potent prior to treatment, 4 reported erectile impotence after radiotherapy (23.5%). One rectovesical fistula (2.5%) 2 cases of necrosis of the prostate after therapy (5.0%) 4 acute cases of proctitis (10%) 4 acute cases of urethritis (10%) 32 acute cases of gross hematuria (80%)
Teh et al., 1998 (47) n=30	• Brachytherapy for Salvage Therapy Acute GU, 7/30 patients experienced grade 1 4/30 patients experienced grade 2 Acute GI, 3/30 patients experienced grade 1 1/30 patients experienced grade 2 Late GU, 2/ 30 patients experienced grade 2 Late GI 1/30 patients experienced grade 2
Grado et al., 1999 (15) n=49	• Brachytherapy +/- EBRT for Salvage Therapy One patient of 20 potent before treatment reported decreased capacity for sexual activity Acute urinary symptoms such as frequency, urgency, hesitancy, and nocturia common during the first 3 months 7 patients (14%) received post treatment TURP 95 had had previous TURP) 2 patients (4%) experienced persistent gross hematuria Significant post treatment pain in the form of penile dsysuria in 3 (6%) of patients 2 patients (4%) developed rectal ulcers 1 patients (2%) underwent colostomy for rectal bleeding Incontinence developed in 3 patients (6%) after undergoing TURP

Appendix A: Methodology

The Cochrane Library was searched using 'brachytherapy with the restriction date=new (ie. only from the latest update to the Library, i.e. Version 3)', MEDLINE (via PubMed) was searched using 'brachytherapy & prostat*' with the date limit 1997-August 1999. HealthSTAR (via Internet Grateful Med) was searched using 'brachytherapy and prostatic neoplasms / human limit / MEDLINE references excluded' with the date range 1992-August 1999. CancerLit (via NCI) was searched for 'brachytherapy and prostat*' for the dates 1997- August 1999. EMBASE and CINAHL were searched for 'brachytherapy and prostate cancer / limited to human studies' for 1997- April 1999.

The search results were screened, first by title and then by abstract, and the literature thought to be the most relevant was obtained. There was particular interest in papers reporting patient outcomes following brachytherapy and in those providing comparisons with other therapeutic approaches. Reference lists in retrieved literature were also screened, and the most relevant references from them were ordered. Information about Prostate Cancer and Brachytherapy was also obtained on the World Wide Web using the Infoseek search engine.

In this report:

Efficacy refers to the performance of a technology under 'ideal' conditions or conditions of best practice; and

Effectiveness refers to the performance of a technology under 'routine' conditions, for example when it has become widely distributed in a health care system.

Appendix B: Earlier studies of brachytherapy

The following table is taken from the earlier publication by the Foundation (2) and summarises relevant studies reported in the literature to mid-1997.

Table 3: Studies on brachytherapy for prostate cancer

Study	Subjects	Methods	Results	Authors' conclusions
Adolfsson et al. (1)	▪ n = 37 ▪ median age 68 years ▪ prostate cancer of all grades	▪ I-125 seed implants (digitally guided) ▪ mean follow-up 62 +/- 19 months	▪ at most recent follow-up, 18 clinically free of the disease, 11 deaths (9 from prostate cancer) ▪ complications in 24 patients (urgency, proctitis, rectal complications, sepsis)	Digitally directed retropubic implantation of I-125 appears inferior to other treatments of clinically confined prostate cancer both regarding outcome as well as complication rate.
Arterbery et al. (3)	▪ n = 21 ▪ stage A and B prostate tumors	▪ I-125 seeds (approx. 75 per patient with an average activity of 0.62 mCi/seed) ▪ CT-guided implantations ▪ follow-up 6 to 12 months	▪ substantial dysuria, nocturia and frequency in first 2 to 24 weeks, resolved within 4 to 6 months ▪ 94% of patients potent before surgery were potent 1 year after ▪ elevated PSA levels of 76% of patients with Stage A or B tumors returned to normal within 6 months	Short term tumor responses are encouraging, and CT-guided transperineal prostate implants entail moderate, temporary urinary and rectal morbidity.
Beyer & Priestley (4)	▪ n = 499 ▪ T1 or T2 node-negative adenocarcinoma of the prostate	▪ I-125 seeds and 160 Gy ▪ 10 patients lost to follow-up in 1st year ▪ clinical status and PSA levels recorded before and after treatment ▪ median follow-up 35 months (range 3 to 70 months)	▪ clinical local control rate of 83%. (correlated with tumor stage and grade) ▪ at 5 year follow-up, the biochemical disease-free rate ranged 30% to 94%, and was correlated with tumor stage, tumor grade, and PSA at presentation ▪ few complications (urinary urgency, dysuria, incontinence, proctitis)	Permanent implantation of I-125 seeds is a viable alternative for patients with early-stage and low- to moderate-grade cancers. The PSA provides significant prognostic information and aids in case selection. Better management options are needed for high grade and bilateral tumors

Table 3: Studies on brachytherapy for prostate cancer (cont'd)

Study	Subjects	Methods	Results	Authors' conclusions
Blasko et al. (5)	▪ 197 patients with clinical stage T1 and T2 prostatic carcinoma ▪ Pretreatment serum PSA levels elevated (greater than 4.0 ng/mL.) in 138 patients (70%). ▪ 105 well differentiated (Gleason score 2 to 4), 87 moderately differentiated (Gleason score 5 to 6) and 5 indeterminate tumors	▪ I-125 implantation (total dosage implanted ranged from 15 to 62 mCi, and prescribed minimum prostatic dose was 160 Gy) ▪ median follow-up 3 years (range 1 to 7 years)	▪ elevated PSA levels returned to normal in 98% of 138 with high PSA ▪ trend for higher failure rates for patients with higher pre-treatment PSA levels, higher Gleason scores, or higher stages of cancer. ▪ actuarial rate of increasing PSA or clinical failure 7% at 5 years.	There is a high rate of clinical and chemical freedom from progression following I-125 implantation for carefully selected patients with early stage prostatic carcinoma. (Patients with minimal likelihood of extra capsular extension).
Chaikin et al. (7)	▪ mean age = 69 years (54 to 82) ▪ potent brachytherapy group mean age = 70 years (56 to 83)	▪ cryosurgical ablation of prostate (CSAP) (n=28), or interstitial radiotherapy (brachytherapy) (n=37) ▪ CSAP group followed up at 12 months, and brachytherapy group followed up at 18 months ▪ follow-up = questioning patients about their sexuality over the telephone	▪ 71% of the CSAP patients were potent preoperatively, and 10% at follow-up ▪ 73% of the brachytherapy patients were potent preoperatively, and 55% at follow-up ▪ all of the patients who reported potency felt that the quality of their erections had decreased following radiation	Short- term results with brachytherapy and CSAP suggest a significant adverse effect on erectile function. Results suggest that enhanced preservation of potency should not be used as an enticement in the promotion of brachytherapy or CSAP
D'Addessi et al. (9)	▪ intraglandular prostate cancer ▪ n = 63	▪ I-125 seed implantation and pelvic lymphadenectomy ▪ follow-up at 10 years	▪ at 10 years overall survival for T1 and T2 stages is 71% and 57% respectively; for G1, G2 and G3 grades 84%, 54% and 44% ▪ local recurrences, complications and side effects compared to data from other sources following EBRT and radical prostatectomy; - the survival results are similar, but the incidence of complications is lower following implantation.	I-125 seed implantation could offer patients, who are often young and asymptomatic, satisfactory chances of survival and a very high quality of life.
Dattoli et al. (12)	▪ n = 73 ▪ T2A-T3 prostatic carcinoma treated 1991-94 (specify risk factors)	▪ 41 Gy ▪ EBRT and Pd-103 boost (80 Gy)	▪ Actuarial freedom from biochemical failure at 3y was 79%	EBRT and Pd-103 compare favorably with EBRT only

Table 3: Studies on brachytherapy for prostate cancer (cont'd)

Study	Subjects	Methods	Results	Authors' conclusions
Glajchen et al. (14)	▪ n = 96 ▪ patients who had undergone radioactive seed implantation of the prostate gland with and without laparoscopic lymph node dissection	▪ retrospective review of CT scans of the pelvis	▪ 42 of 73 patients who underwent lymph node dissection had low-attenuation masses along lymph node chains, compared with 1/23 who did not ▪ 14 patients had fluid collections within the pelvis, 13 of whom had undergone lymph node dissection ▪ other imaging findings included ectopic seeds (10 patients) and subcutaneous and intrapelvic air (11 patients).	Radiologists should be aware of these findings from I-125 seed implantation and lymph node dissection.
Grossman & Thompson (17)	▪ n = 100 ▪ stage B or C prostate carcinoma ▪ implanted 1970-1974 ▪ review of records.	▪ bilateral pelvic lymphadenectomy and retropubic implantation of I-125 seeds ▪ preoperative patient history and physical examination, excretory urography, cystoscopy and bimanual examination, acid and alkaline phosphatase measurements, and skeletal survey (56 patients) or bone scan (44 patients). ▪ follow-up for 5 plus years (98 patients)	▪ 5- and 9-year survival rates of 83% and 52% ▪ variables associated with longer survival included low tumor stage (an intraprostatic nodule confined to one lobe), good-to-moderate differentiation, and absence of nodal metastasis	Variables associated with longer survival after I-125 implantation and pelvic lymphadenectomy include low tumor stage, good to moderate differentiation, and absence of nodal metastasis
Hochstetler et al. (18)	▪ n = 177 ▪ adenocarcinoma of the prostate ▪ 12% A2, 15% B1, 34% B2, 38% C ▪ 20 had pelvic lymph node involvement so were excluded from this review	▪ transcutaneous, transperineal Au-198 seeds ▪ median radioactivity dose of 164 mCi ▪ median follow-up of 48 months	▪ cancer-specific survival at 5 years was 100% for stage A2 and B1, 90% for stage B2, and 76% for stage C cancer ▪ significant complications in 2 patients	Survival rates of patients treated with Au-198 seed implantation for localized cancer are equivalent or better when compared to historical data of patients treated with I-125 implantation, EBRT, combination Au-198 implantation and EBRT, and radical prostatectomy. In addition, these comparable survival rates using interstitial Au-198 seeds may be achieved with less morbidity.

Table 3: Studies on brachytherapy for prostate cancer (cont'd)

Study	Subjects	Methods	Results	Authors' conclusions
Kaye et al. (21)	▪ n = 76 ▪ group 1 (n=45) smaller, more well differentiated tumors, usually 2 cm diameter on DRE or TRUS and a 7 Gleason score. ▪ group 2 (n=31) localized tumors > 2 cm. in diameter and/or a Gleason sum $\geq$ 7	▪ group 1 = I-125 alone ▪ group 2 = low dose EBRT followed by I-125 boost 4 weeks later ▪ mean follow-up = 26.3 months ▪ procedures were performed on an outpatient or short stay basis	▪ complete clinical progression-free survival, including PSA,DRE and biopsy, was 51% for group 1 and 63.3% for group 2 ▪ PSA progression-free survival was 97.7% for group 1 and 94.7% for group 2 ▪ the procedures were well tolerated with good potency sparing	Appears to be superior to EBRT only, though longer follow-up is needed to substantiate these favorable early results. The procedures provide a good alternative to EBRT only or hormonal treatment for select patients with localized prostate cancer who may not be candidates for radical prostatectomy.
Kaye et al. (20)	▪ n = 86 ▪ stages T1-T3 prostate adenocarcinoma ▪ group 1 = smaller more well differentiated cancers ▪ group 2 = larger less well differentiated tumors. (Similar patient group to previous study).	▪ group 1 = I-125 implant alone ▪ group 2 = low dose EBRT followed by I-125I boost ▪ mean follow up = 26.1 months (range 11 to 60) ▪ follow-up = regular PSA and DRE evaluations. ▪ 80 patients had a biopsy at 1 year, PSA progression-free survival determined, complications and potency were assessed.	▪ not discussed in abstract	Early results of I-125 prostate seed implantation are very promising especially for selected cases of localized carcinoma.
Kleinberg et al. (23)	▪ n = 31 ▪ stage T1 or T2 prostatic carcinoma	▪ CT -guided transperineal I-125 implants (median total activity = 47 mCi -- range = 35-73 mCi)	▪ post-treatment complications within 2 months (nocturia 80%, mild dysuria 48%, rectal urgency 25%, rectal bleeding or ulceration 47%, and discomfort during ejection or ejaculation for 5/18 ▪ complications were temporary and not in need of major treatment in most cases	I-125 implantation, as performed in this series, is generally associated with only mild to moderate genitourinary and rectal symptoms that may persist 6 months or more after implantation.
Lannon et al. (25)	▪ n = 180 ▪ A2-C prostate cancer treated between 1976 - 1988 ▪ follow-up data on 164	▪ pelvic lymphadenectomy and Au-198 and EBRT	▪ actuarial 10 y cancer free survival rates 83.0% and 91.3% for stages A2 and B1 ▪ positive biopsy 13% at 2 y and 17.1 % at 5y	Au-198 and EBRT valid option for patients with localized prostate cancer

Table 3: Studies on brachytherapy for prostate cancer (cont'd)

Study	Subjects	Methods	Results	Authors' conclusions
Leibel et al. (26)	▪ n = 1078 ▪ stage B-C node negative (733) or node positive (345) carcinoma of the prostate. ▪ treatment between 1970 and 1985.	▪ pelvic lymph node dissection and I-125 implantation ▪ follow-up 15 years	▪ 15-year actuarial distant metastases-free survival rate for the entire group of was 27% ▪ lymph node involvement was the most significant covariate affecting distant metastases-free survival, although local failure, stage, and grade were also independent variables	Essentially all node-positive patients with carcinoma of the prostate will develop distant metastatic disease if followed for sufficiently long periods of time. This is consistent with the hypothesis that in such patients distant micrometastatic dissemination already exists at the time of initial diagnosis. The data suggest that clinical trials designed to test whether improvements in local therapy impact on survival should be restricted to node negative patients. The data also raise concerns regarding the therapeutic value of elective whole pelvic irradiation.
Loening & Turner (27)	▪ n = 31 ▪ patients who failed prior EBRT	▪ percutaneous transperineal placement of Au-198 seeds ▪ follow-up 12 months	▪ of 15 patients biopsied at 12 months after treatment, 4 (27%) were positive, 6 (40%) were negative, and 5 (33%) showed prostate cancer with radiation changes. ▪ two of three patients have died of prostate cancer, with an overall 5-year estimated survival of 67%	Interstitial brachytherapy was an additional well-tolerated treatment modality in this group of 31 patients.
Nag et al. (29)	▪ n = 32 ▪ Stage A or B prostate carcinoma	▪ implanted transperineally with Pd-103 using TRUS and fluoroscopy ▪ median follow-up 20 months (range 2 to 45 months)	▪ mild and transient dysuria in 88%, moderate to severe dysuria in 18%, mild rectal symptoms in 19% ▪ 7 of the 3,213 seeds implanted (0.2%) migrated to the lung in 6 of 30 patients, but did not cause clinical problems	Pd-103 prostate brachytherapy generally associated with only mild or moderate urinary and rectal symptoms, and the incidence of severe complications is low. Further follow-up is required to evaluate the efficacy.

Table 3: Studies on brachytherapy for prostate cancer (cont'd)

Study	Subjects	Methods	Results	Authors' conclusions
Prestidge et al. (33)	▪ n = 402 with early stage prostatic carcinoma ▪ 201 evaluated post-operatively ▪ median follow-up 40 months (range 12-83)	▪ I-125 prescribed to a MPD of 160 Gy with a median activity of 35.5 mCi (n=143) or Pd-103 prescribed to a MPD of 115 Gy with a median activity of 123 mCi (n=58) ▪ median follow-up biopsy 40 months (range: 12-83 months)	▪ at the time of last biopsy, 161 (80%) had negative pathology, 34 (17%) were indeterminate, and 6 (3%) were positive.	These results support the use of modern interstitial brachytherapy techniques for selected patients with early stage adenocarcinoma of the prostate.
Roeleveld et al. (37)	▪ n = 75 ▪ T1 or T2 carcinoma of the prostate, prostatic volume < 40 mL, no contraindications to surgery	▪ retrospective review of records 1981-1990 ▪ I-125 seed implantation preceded by pelvic lymph node dissection ▪ median follow-up 103 months (range 60-157 months)	▪ major complications in 23%, residual carcinoma or distant metastases in 61%. ▪ 16 patients died from prostatic carcinoma. ▪ 5- and 10-year survival rates of 74% and 42%, respectively, and cancer-specific 5- and 10-year survival rates of 85% and 67%	Treatment of carcinoma of the prostate with retropubic implantation of I-125 seeds resulted in a high incidence of local therapeutic failure and numerous postoperative complications. These results are poorer than those of total prostatectomy and EBRT.
Stock et al. (39)	▪ n = 97 ▪ T1 to T2 adenocarcinoma of the prostate ▪ 79 had negative laparoscopic pelvic lymph node dissections prior to implantation, and patients with positive lymph nodes were not implanted.	▪ permanent implantation of I-125 in 71 patients and of Pd-103 in 26 ▪ median follow-up of 18 months (range: 6-51 months). ▪ transrectal prostate biopsies were performed 18 to 36 months post-treatment in 39 patients	▪ 76% freedom from PSA failure at 2 years, correlation with tumor stage and pre-treatment PSA ▪ negative biopsies in 74% of the 39 ▪ 96% and 79% preservation of erectile function and sexual potency at 2 years ▪ minimal renal complications	Interactive, ultrasound-guided transperineal brachytherapy results in a low PSA failure rate, high negative biopsy rate, and is associated with low morbidity and preservation of erectile function.
Stock et al. (40)	▪ n = 89 ▪ localized prostate cancer (T1-T2)	▪ I=125 seed implantation in 73 patients with a combined Gleason grade of 2-6 ▪ Pd-103 seed implantation in 16 patients with higher grade lesions ▪ median follow-up 15 months (range 1.5-52 months) ▪ sexual potency was assessed prior to implantation, and at 3 and 6 months, and then every 6 months implantation ▪ Erectile function was graded	▪ 2.5% impotency at 1 year and 6% impotency at 2 years. ▪ only 2 patients became impotent following treatment (at 1 year and at 16 months) ▪ sexual function rates had decreased for 29% at 1 year and 39% at 2 years.	Interactive ultrasound-guided transperineal brachytherapy for the treatment of localized prostate cancer is associated with preservation of erectile function in the vast majority of patients, although a minor decrease in potency is not uncommon.

Table 3: Studies on brachytherapy for prostate cancer (cont'd)

Study	Subjects	Methods	Results	Authors' conclusions
Stone & Stock (42)	▪ n = 71 ▪ T1b-T2c prostate carcinoma	▪ ultrasound-guided I-125 seed plantation in 60, and 103Pd implantation in 11. ▪ a laparoscopic lymph node dissection was performed in 58 patients. ▪ mean follow-up of 2 years (range 1 to 4.2 years).	▪ freedom from PSA failure rates was related to pre-treatment PSA level ▪ 82% negative biopsy rate at 18 to 24 months, related to pre-treatment PSA ▪ urinary retention in 5.6%; preserved potency in 94%	The real-time ultrasound-guided transperineal seed implantation technique is an effective and safe method of treating prostate cancer. Longer follow-up is needed to substantiate these early encouraging results.
Stromberg et al. (45)	▪ n = 57 ▪ bulky prostate carcinoma (5 x B2, 52 x C0	▪ EBRT, lymphadenectomy then Ir-192 and EBRT ▪ 92% had hormonal treatment post-therapy	▪ 5 y actuarial survival rate 85%, disease free survival 63% (5 y survival 93% with negative nodes, 79% with positive)	Results suggest that bulky prostate carcinoma can be successfully controlled locally by this aggressive approach with moderate toxicity and improved survival
Vijverberg et al. (48)	▪ n = 52 ▪ localised prostate cancer	▪ transperineal ultrasound-guided I-125 implantation ▪ follow-up biopsies from previously malignant areas every 6 months	▪ the percentage of negative biopsies increased from 22% at 6 months to 50% at 48 months ▪ implant quality was analysed in 37 patients – 43% had good implants, 35% had moderate implants, and 22% had poor implants ▪ significant correlations were observed between implant quality and negative biopsy, between implant quality and serum PSA, and between volume reduction and serum PSA	In the future, quality of implantations should be analyzed to identify suboptimal implants and perhaps perform a 2nd implant; Longer term follow-ups and larger groups are needed to determine if there are radio-resistant clones of tumors.
Wallner et al. (51)	▪ n = 19 ▪ stage T1-T2 prostatic carcinoma ▪ prior TURP	▪ I-125 or Pd-103 implantation ▪ median follow-up = 3 years (range 1 to 6 years) ▪ time from TURP to implantation ranged from 2 months to 15 years (median: 3 years)	▪ mild urinary incontinence in 1 patient at 6 months ▪ 94% freedom from urinary incontinence at 3 years ▪ all patients potent pre-surgically were still potent 3 years after surgery	There is remarkably little adverse sequelae following I-125 or Pd-103 implantation in patients with a prior history of TURP.

Table 3: Studies on brachytherapy for prostate cancer (cont'd)

Study	Subjects	Methods	Results	Authors' conclusions
Wallner et al. (49)	▪ n = 92 ▪ prostatic cacinoma (stage T1 or T2, and Gleason score 2 to 7/10)	▪ CT-based transperineal I-125 prostate implantation (prescribed minimum radiation dose was 140 to 160 Gy) ▪ median follow-up = 3 years (range 1 to 7 years)	▪ in 46% radiation-related urinary symptoms were substantial enough at 1 month following implantation to require medication ▪ two years after implantation, 15% of patients had persistent urinary symptoms ▪ 8% underwent TURP at 2 years; 5 developed rectal ulcerations ▪ 63% had freedom from biochemical failure at 4 years ▪ strongest predictor of failure was pre-treatment PSA; Gleason score and tumor stage also correlated with post-treatment failure	The 5-year biochemical freedom-from-progression rates following transperineal I-125 implantation are comparable with those achieved with prostatectomy. The morbidity has decreased with increased physician experience.
Wallner et al. (50)	▪ n = 62 ▪ stage T1 or T2 prostatic carcinoma	▪ outpatient, CT-based transperineal I-125 prostate implantation (median: 47 mCi). ▪ median follow-up 19 months (range 6-55 months)	▪ 96% of patients with elevated PSA levels had normal PSA levels within 24 months of treatment. ▪ 17% had chemical (rising PSA) or clinical failure at 3 years ▪ 81% potent pre-surgically remained potent at 3 years ▪ 5 patients developed radiation-induced rectal ulcerations 11-22 months following implantation, and 3 required a TURP	The short-term clinical and chemical freedom-from-progression rates following I-125 implantation are comparable to that achieved with prostatectomy, with high preservation of sexual potency and moderate morbidity.
Weyrich et al. (53)	▪ n = 132 ▪ 1975-1985 ▪ localized prostate carcinoma ▪ surgical stages A (29%), B (64%), C (9%), D1 (18%)	▪ bilateral pelvic lymphadenectomy and insertion of I-125 seeds	▪ less than 33% had short or long-term complications ▪ 10 year survival rates for evaluable patients from 44% to 75%, and were related to tumor stage ▪ 10 year disease-free rates ranged from 25 to 67%, also related to tumor stage	Interstitial radiotherapy may play a role in the treatment of nonsurgical candidates with low volume and well- to moderately-differentiated adenocarcinoma of the prostate.

Table 3: Studies on brachytherapy for prostate cancer (cont'd)

Study	Subjects	Methods	Results	Authors' conclusions
Zelefsky et al (55)	▪ n = 403	▪ pelvic lymph node dissection and retropubic radioactive I-125 implantation ▪ follow-up 5 years	▪ 5 year relapse free survival rate ranged from 27 to 85%, and was dependent upon initial PSA ▪ tumor grade also affected the findings	Continuously maintained PSA levels around 1.0 ng/mL may serve as an end point for early evaluation of the efficacy of experimental radiotherapy protocols in prostate cancer.

Appendix C

D'Amico et al. 1998 (11)

Biochemical Outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized cancer.

 # Patients: 1872 patients RP 888
Brachytherapy +/- androgen deprivation 218
EBRT 766

Outcome Measurement Definition: PSA failure: three consecutive rising PSA values each obtained at least 3 months apart. Time of failure was defined as the mid-point between the time of the PSA nadir value and the time of the first rising PSA value.

Follow-up Time (median): 888 surgical patients at HUP follow-up of 38 months (8-100):
766 radiation patients at the Joint Center for Radiation Therapy 38 months (8-75)
218 interstitial radiation +/- hormonal therapy managed patients at HUP 41 months (3-72)

Patient Age (median): N/A

Treatment Time Frame (Dates): January 89 – October 1997

Treatment:

RP and brachytherapy +/- androgen deprivation therapy: Hospital of the University of Pennsylvania, Philadelphia

EBRT: Joint Center for Radiation Therapy, Boston, Mass.

Surgical treatment consisted of a radical retropubic prostatectomy and bilateral pelvic lymph node sampling.

BT: 103Pd, perineal template guided, peripheral-loading technique, transrectal ultrasound unit. Minimum peripheral dose 115 Gy.

Total amount implanted ranged from 1306 to 7189 MBq.

Of 218 who received brachytherapy, 152 (70%) received neoadjuvant androgen deprivation for a median of 3 months (2-10 months)

EBRT: conformal

Patients with T1c, T2a disease, and PSA 10ng/mL or less, Gleason 2-6: median prescription dose 66 Gy (66-70 Gy), was delivered using 2 Gy fractions to prostate only with 1.5 cm margin.

Remainder of patients: median prescription dose of 45 Gy (45-50.4 Gy) in 1.8 Gy fractions to the prostate and seminal vesicles plus 1.5 cm margin, + 22 Gy (18-22Gy) in 1.8 – 2.0 Gy fractions to prostate alone

Patient Profile

Patients stratified by Gleason score, PSA, and T stage

Patients with clinical stage T1a, T1b were not managed using brachytherapy because of the significant rate of urinary incontinence noted in patients with prior TURP. Therefore T1a, T1b disease managed with RP or EBRT were excluded from the study to ensure statistically valid comparisons.

Low risk group: T1c, T2a, and PSA of 10 ng/mL or less, and Gleason 6 or less (<25% risk of failure at 5-y)

Intermediate risk group: PSA levels higher than 10, less than 20 ng/mL, Gleason of 7, clinical stage T2b (25-50% at 5-y post-therapy of PSA failure)

High risk: T2c disease, or PSA level of more than 20 ng/mL, or a biopsy Gleason score of 8 or more (50% risk of failure at 5-y)

Study Design: Retrospective
Patients treated at 2 different institutions

Results
95% confidence intervals

No significant difference ($p \geq 0.25$) in outcome was noted in low risk patients across all treatment modalities.

High risk patients treated using RP or EBRT did significantly better ($p \leq 0.01$) than those managed with brachytherapy with or without neoadjuvant androgen deprivation.

Intermediate risk patients did significantly worse ($p \leq 0.003$) if managed by brachytherapy alone, but fared equivalently to RP if androgen deprivation was also administered ($p \leq 0.18$).

Results are relative risk compared to RP of actuarial PSA failure at 5 years.
Low risk group: EBRT 1.1
Brachytherapy plus androgen deprivation therapy 0.5
Brachytherapy alone 1.1

Intermediate risk group: EBRT 0.8
Brachytherapy plus androgen deprivation 1.6
Brachytherapy alone 3.1

High risk group: EBRT 0.9
Brachytherapy plus androgen deprivation 2.2
Brachytherapy alone 3.0

Complications: N/A

Comments
Direct comparison of the results of ultrasound-guided interstitial prostate radiation therapy with RP or EBRT stratified by the pretreatment prognostic factors has not been previously reported.

Cox regression multivariable analysis was used to compare PSA outcome among the therapies within each risk group.

Coefficients from the Cox analysis were used to calculate overall risk of PSA failure in each group.

RP defined as baseline (Risk =1).

High risk patients managed with brachytherapy plus neoadjuvant androgen deprivation had an increased proportion of patients with PSA levels lower than 10 ng/mL and decreased proportion of patients with a PSA level of more than 20 ng/mL compared with patients managed with RP or EBRT. Both of these differences could bias the comparisons of PSA survival in favour of the brachytherapy plus neoadjuvant androgen suppression patient cohort.

Results also stratified according to Gleason – similar results.

Intermediate to high risk patients would combine brachytherapy with EBRT to treat cancerous cells beyond the prostate. This treatment is not considered in this study.

No measure of brachytherapy quality – CT based dosimetric analysis

Some subsets of patients contain too few of numbers to be more than preliminary i.e. Intermediate risk brachytherapy at 2 y.

Zelefsky *et al.* 1999 (56)

Comparison of the 5-Year Outcome and Morbidity of Three-Dimensional Conformal Radiotherapy Versus Transperineal Permanent Iodine-125 Implantation for Early-Stage Prostatic Cancer.

 # Patients: 282
Outcome Measurement Definition: Three successive PSA elevations observed from the post-treatment nadir PSA value

Follow-up Time (median): CRT 36 months (12-109)

Brachytherapy 24 months (6-103)

Patient Age (median): 68 and 64 respectively

Treatment Time Frame (Dates): 1989-1996

Treatment:
137 patients treated with 3D CRT
145 patients treated with brachytherapy
CRT median dose 70.2 Gray
brachytherapy median dose 150 Gy

Brachytherapy
Pre-implantation CT scan and computer aided optimization method used to determine needle placement, number of sources, and respective locations.

Fluoroscopy was used to monitor needle placement during the implantation procedure.

Ultrasound guidance not routinely used.

Prescribed minimum dose to the prostate 140-160 Gy.

Median value of implanted activity 45mCi of 125I (range 32-77).

Neoadjuvant androgen deprivation was given to 16 patients(11%) in this group for a median duration of 2 months before brachytherapy.

3D-CRT

Dose 64.8-81.0 Gy, in daily doses of 1.8 Gy
23 patients (17%) treated with neoadjuvant androgen deprivation for 3 months, ended at same time as radiotherapy ended.

Patient Profile
Patient Parameters: pretreatment PSA less than or equal to 10.0ng/mL, Gleason score of 6 or lower, and stage less than or equal to T2b.

Of 743 patients treated with 3D-CRT, 137 or 18% were characterized as having favourable prognostic features and used for this analysis.

Of 245 patients who received brachytherapy, 145 (58%) were characterized as having favourable prognostic features, and used for this analysis.

Favourable prognostic features include PSA less than or equal to 10.0 ng/mL, Gleason score of 6 or lower for 3D-CRT, and lower than 7 or lower for brachytherapy, less than or equal to stage T2b disease.

Study Design: Retrospective
Brachytherapy vs. 3D-CRT
Favourable risk patients chosen

Results:
11 patients (8%) in the CRT group, and 12 patients (8%) in the brachytherapy group developed a PSA relapse.

Median time to biochemical failure in the CRT and brachytherapy groups were 25 and 20 months respectively.

5 year actuarial PSA relapse-free survival rates of 88 and 82% respectively.

Multivariate analysis could not indicate mode of therapy had an impact upon biochemical outcome in these patients.

Complications:

CRT:
80 patients 58% had no or only mild (grade 1) acute gastrourinary toxicity
57 patients (42%) grade 2 urinary symptoms requiring medication

124 (91%) had minimal to no late GU toxicity
11 patients (8%) had late grade 2 urinary symptoms
2 patients (1%) late grade 3 urinary toxicity (urethral stricture)

Brachytherapy:
5 (3%) had acute urinary retention (grade 3)

no grade 4 urinary toxicity observed in either group.

90 (62%) had minimal to no late GU toxicity
Grade 2 urinary toxicity that persisted more than 1-y 45 patients(31%).
10 patients (7%) late grade 3 urinary toxicity (urethral stricture)

no late grade 4 urinary toxicity observed in either group

Rectal toxicity
CRT:
118 (86%) had no or mild (grade 1) acute gastrointestinal toxicity
19 (14%) had grade 2 requiring medication.
157 (94%) minimal to no late rectal toxicity
10 patients (6%) had late grade 2 GI toxicity (rectal bleeding)

Brachytherapy
No acute rectal symptoms
139 (96%) had minimal to no late rectal toxicity
6 patients (4%) experienced late grade 2 GI toxicity (rectal bleeding).

Impotence
Among patients who were potent before treatment
CRT
32 /101 (32%) become impotent

Brachytherapy
28/132 (21%) became impotent following therapy

Higher radiation dose risk factor for impotence

Comments:
These are favourable risk patients
Unusually high impotence for brachytherapy

King et al., 1998 (22)

Definitive therapy for stage T1/T2 prostate carcinoma: PSA-based comparison between surgery, external beam, and implant radiotherapy

 # Patients: 221 total
73 RP
85 EBRT
63 brachytherapy

Outcome Measurement Definition: Biochemical disease-free survival (bNED) PSA level less than 0.1 ng/mL for RP, 1.0 ng/mL or less for EB and IMP
Kaplan-Meier product limit analysis

Follow-up Time (median): 13 months brachytherapy
20 months EBRT
31 months RP

Patient Age (median): 66 brachytherapy
72 EBRT
62 RP

Treatment Time Frame (Dates): brachytherapy: since late 1992
EBRT: between 1990 and 1995
RP: 1990-1994

Treatment:

Brachytherapy: transrectal ultrasound guided transperineal implant.
minimum dose 160 Gy with I125
115Gy to the 4 patients receiving Pd103

External Beam: mean of 66 Gy via 1.8 to 2 Gy fractions. No prior or concurrent hormone deprivation therapy

Radical prostatectomy: radical retropubic prostatectomy . No hormone deprivation therapy.

Patient Profile

Represent a subset of patients with PSA ≤ 20 ng/mL, Gleason 8 or less.
Median Gleason 6 for all 3 groups
Mean PSA 7.9 for IMP
9.7 EB
8.9 RP

Brachytherapy group had significantly less T2a disease, and proportionately more T1c than RP or EB, i.e. less advanced clinical stage.

RP patients pathologically NO

Brachytherapy patients chosen for 6 months or longer follow-up, no hormone deprivation therapy, and no external beam radiotherapy.

Brachytherapy group contained only 24% with iPSA ≥10ng/mL, while the EB and RP groups had 42 and 38% respectively. Since iPSA is strong indicator of biochemical success, this is a weakness of this study.

Study Design

Retrospective

Choice of treatment determined by patient preference, referring physician, or exclusion.
i.e. non-randomized
Single institution RP/IMP/EB

Results:

Actuarial bNED at 48 months:
All patients: RP 69.9%
IMP 60.3%
EB 43.5%

iPSA ≤10ng/mL
RP 75.6%
IMP 66.7%
EB 51.0%

Complications:

Brachytherapy group: minor urinary tract morbidity common
Occasional rectal morbidity, non grade 3 or higher
No TURP required or urinary incontinence

Comments:

This study favours brachytherapy or radical prostatectomy over external beam therapy. No significant difference between RP and IMP. Patient population differences make interpretation difficult though.

Koutrouvelis 1998 (24)

Three-dimensional stereotactic posterior ischiorectal space computerized tomography guided brachytherapy of prostate cancer: a preliminary report.

 # Patients: 130 patients

Outcome Measurement Definition: PSA levels < 2.0 ng/mL

Follow-up Time (median): ranges from 6 to 24 months: no breakdown.

Patient Age (median): 71 **(**49-90)

Treatment Time Frame (Dates): Previous two years

Treatment:

Computerized tomography
3-D stereotactic system for needle placement
Pd 103 (112000cGY), I125 (16000cGy)
Hormone therapy: 35 treated 1 month to 2 years before brachytherapy, and 2 to 3 months after brachytherapy

Patient Profile
Clinical stage A,B or C adenocarcinoma
Gleason score 2-9
Pretreatment PSA range: 0.9-143ng/mL, mean 16.25, median, 13.0
Initial PSA >10 in 55% of patients
Range of prostate volume: 30-156 cm 3, median 62, mean 65.

Study Design
retrospective
non randomized
no control

Results:
PSA levels decreased to below 2 ng/mL at last follow-up in 95% of patients: no breakdown.
Urinary obstruction improved in all patients: no numbers

Complications:
No hematoma or infection following procedure
No incontinence complications
12% had radiation urethritis, cystits and / or proctitis, lasted for less than 1 month
6% had grade 2 complications for 1-4 months required alpha blockers
no evidence of rectal ulceration or fistula
95% maintained ability for erection.

Comments:
More technique presentation than clinical trial

Poor outcome details, questionable outcome benchmark of 2 ng/mL

CT approach not limited by prostate volume, as compared to TRUS, or public arch interference, or urinary obstruction, or transurethral resection of the prostate

Sharkey et al. 1998 (38)

Outpatient ultrasound-guided palladium 103 brachytherapy for localized adenocarcinoma of the prostate: a preliminary report of 434 patients

 # Patients: 474 patients surveyed, 434 had sufficient data for this report

Outcome Measurement Definition
Biopsy
PSA less than 1.5ng/mL at 1y/2y
Failure: three serial rises above the nadir or a positive biopsy
Success: stable PSA level less than 1.5ng/mL or a negative biopsy.

Follow-up Time (median): Mean 2.3 years (up to 5 years)

Patient Age (median): 73 (52-83)

Treatment Time Frame (Dates): December 91 – July 96

Treatment:
Pd 103 implantation (11 500 cGy)
Preoperative neoadjuvant leuprolide and flutamide given selectively to reduce prostate size greater than 50cc and for Gleason grade lesions greater than 7
224 Pd103 monotherapy
210 Pd103 plus neoadjuvant hormonal therapy

Patient Profile
Patients with positive lymph nodes excluded from study
Average preoperative PSA 7.4ng/mL range 0.1(hormone prior to referral) to 48.8ng/mL
95% were clinically stage 2
Gleason score ranged from 2-10, with 74% having scores less than 7

Study Design: Retrospective
No control group

Results:
Patients with a negative biopsy at year 2:
Pd monotherapy: 90%
Brachytherapy + hormone therapy: 89%
Total patients: 89%

Patients with PSA values less than 1.5ng/mL (year 4, n=81)
Monotherapy: 81%
Brachytherapy + hormone therapy: 79%
Total patients: 80%

(year 1, n=425)
Monotherapy: 76%
Brachytherapy + hormone therapy: 86%
Total patients: 81%

Complications:
Most patients had some degree of short-term bladder and bowel irritation, which required only symptomatic treatment.

Incontinence resulted in less than 5% of patients, and only in those with previous TURP
Impotence occurred in less than 15% of patients.

Comments:
Outpatient setting, requires 1 hr to perform

Storey et al. 1999 (44)

Transperineal 125 iodine implantation for treatment of clinically localized prostate cancer: 5-year tumor control and morbidity

 # Patients: 193 patients available for analysis / 206 treated

Outcome Measurement Definition: Biochemical failure, 3 consecutive rises in PSA, time to failure defined as the average of the time to nadir and the rime to the third rising PSA.
Overall survival
Treatment associated morbidity

Follow-up Time (median*):* 35 months

Patient Age (median): 77 years (63-89)

Treatment Time Frame (Dates*):* August 1988- December 1993

Treatment:
Preplanned ultrasound-guided transperineal brachytherapy
125Iodine Minimum dose 16 000 cGy
No adjuvant hormone treatment

Patient Profile
Had either refused surgery, or were not felt to be good surgical candidates based on overall health

Localized (stage T1 or T2) cancers with low or intermediate grade Gleason score (≤7)

Prostate volume less than 65 cc.

Patients younger than 65 advised to undergo EBRT rather than brachytherapy

PSA ≤4ng/mL 33
PSA >4≤10ng/mL 67
PSA >10ng/mL 83

Study Design: Prospective – probably!

Results:
5-y actuarial biochemical freedom from failure rate for all patients available for follow-up 63%
actuarial 76% in patients with pretreatment PSA ≤10ng/mL
actuarial 51% in patients with values > 10ng/mL
actuarial freedom from failure 84% in patients with pretreatment PSA ≤4ng/mL

actuarial freedom from failure 72% in patients with pretreatment PSA >4,≤10ng/mL

5-y actuarial survival 66%
median actuarial survival was 81 months

post-treatment nadir reached at a median time of 16 months (1-60)

Complications:
Occasional transitory urinary obstructive symptoms
5 patients required long term use of catheter up to 4 months
3 patients reported incontinence
18 reported minor post-brachytherapy dribbling
5 patients persistent hematuria for up to 6 weeks
2 patients developed rectal ulcers 8-10 months following brachytherapy
one patient underwent radical prostatectomy with partial colectomy for prostatic necrosis

Comments:
Approximately 10% of patients in this series had any degree of urinary incontinence after brachytherapy. Authos comment that this compares favorably with the surgical literature that commonly reports incontinence rates of 20-30%.

Ragde et al. 1997 (34)

Interstitial Iodine-125 Radiation without Adjuvant Therapy in the Treatment of Clinically Localized Prostate Carcinoma

 # Patients: 126 patients, 4 died in first 18 months leaving 122 used for study

Outcome Measurement Definition: PSA failure defined as either: PSA progression, 2 consecutive increases from a nadir value, or failure to attain an arbitrary serum PSA value of 1.0 or 0.5 ng/mL at last follow-up.
Post-therapy evaluation included clinical, biochemical (PSA), and pathologic (repeat needle biopsy)
Time to failure measured from the time of implantation to the second PSA elevation

Follow-up Time (median): 69.3 months (average 65.4)

Patient Age (median): 70-y

Treatment Time Frame (Dates): January 88-December 90

Treatment:

^{125}I

Minimum dose 160gray, given 2-5mm beyond the prostate capsule
No androgen deprivation therapy.
Ultrasound unit used for all implants.
Prostate volume determinations performed by step-section planimetry.
Seminal vesicles not included in the treatment plans.
20-48 mCi implanted

Patient Profile
(T1: 23%, T2: 77%)
Pre-biopsy PSA values available for all patients
No surgical staging

Study Design
No controls
Patients treated at different institutions.
not randomized.
Kaplan-Meier method used for statistical appraisal

Results:
No deaths from prostrate carcinoma in this cohort.

7-y Actuarial freedom from PSA progression 89%
7-y Actuarial disease free survival (PSA < 1.0 ng/mL) 87%

7-y Actuarial disease free survival (PSA < 0.5 ng/mL) 79%

Compare their 7-y actuarial results with radical prostatectomy and EBRT results.

Complications:
Most patients experienced some degree of urinary urgency, frequency, and varying degrees of outlet obstruction, which usually subsided within a 5 to 10 month period. Temporary rectal symptoms rarely encountered. Late complications consisted mainly of urinary incontinence and urethral strictures. Of 118 patients followed for a median of 69.3 months post-brachytherapy, 112 patients remained continent of urine, and 6 patients became incontinent. Incontinence was limited to patients who had undergone a TURP. Thus an overall incontinence rate of 5.1% was observed.

Five urinary diversions performed.

Bulbomembranous urethral strictures occurred in 14/118 patients (12%).

Comments:
The 7-year results presented her are excellent and competitive with RP. This combined with its single session, outpatient nature, minimal morbidity, should encourage further evaluation of this treatment for early stage prostatic cancer

There are two subsequent papers that compare results with this paper to “create” comparison studies with radical prostatectomy.

Authors comment on comparison to “average” outcomes from radical prostatectomy and EBRT, quoting references, but not detailing choice of patient population, detailed comparison of complications, etc.

Ramos et al. 1999 (36)

Retrospective comparison of radical retropubic prostatectomy and 125iodine brachytherapy for localized prostate cancer

 # Patients: 299 out of 1364 who met Ragde study criteria / 1952 RPs performed

Outcome Measurement Definition: First confirmed detectable PSA greater than 0.3ng/mL after surgery, histologically confirmed local tumor growth or distant metastases.

Time to recurrence defined as the number of months between the date of surgery and the first evidence of PSA greater than 0.3ng/mL, local recurrence, or distant metastases.

Follow-up Time (median): Mean 60 +/- 35 months

Patient Age (median): mean age 62.3 +/- 7.6 years (S.D.) in final group of 299

Treatment Time Frame (Dates): January 1998-April 1998

Treatment: RP

Patient Profile
Matched for preoperative Gleason score, PSA, and clinical stage to patients in 7 y Ragde study.
96% of 1952 men were white

Preoperative Gleason 2-6
PSA <4, 4.1-9.9, 10-40ng/mL
Clinical Stage T1, T2a, T2b, T2c

Organ confined tumors in 233 patients (78%)
Cancer at the surgical margins in 52 (17%)
Seminal vesicle involvement in 6 (2%)
No lymph node metastases

Study Design: retrospective
non randomized
7 y actuarial survival Kaplan-Meier product limit estimates
5 computer generated random samples of the population used to calculate mean result.
used RP group, and matched them to Ragde 1997 brachytherapy results, same as Polascik et al did, but claim that their RP patients are even more closely matched.

Results:
Recurrence in 35 (11%) in the surgical series, of whom 31 had PSA recurrence only, 1 had local recurrence, 1 had distant metastases, and 2 had local and distant metastases.
7 y probability of non progression was 84% (95% confidence intervals). For RP compared to 79% for similar patients in brachytherapy series.

In brachytherapy found PSA higher than 0.5 ng/mL at last follow-up in 23 patients (19%), including 4 with positive biopsies, and 4 with metastases.

No striking differences in 7 year recurrence-free survival between the 2 series.
Brachytherapy series may have been favorably influenced by it taking 1 y of PSA rises to detect failure, It takes longer to reach a nadir in brachytherapy, thus those patients are not yet at risk for failure.

Complications: N/A

Comments:
RP yields a proportionately but not statistically significant higher 7-year probability of non-progression than 125I brachytherapy inpatients with favourable clinicopathological characteristics.

Comparisons are confounded by residual differences in clinicopathological features of tumors between groups and different treatment end points to determine outcomes.

Polascik et al. 1998 (32)

Comparison of radical prostatectomy and iodine 125 interstitial radiotherapy for the treatment of clinically localized prostate cancer: a 7-year biochemical (PSA) progression analysis.

 # Patients: 76

Outcome Measurement Definition: RP: PSA level greater then 0.2ng/mL is failure – done in this paper

Brachytherapy: PSA greater than 0.5 ng/mL – from Ragde paper 1987. Time to failure defined as from date of surgery to detectable PSA level in years.

Follow-up Time (median): mean 83.2 +/- 22.8 months (12-108)

Patient Age (median): mean 59.4 +/- 5.9 (44-72)

Treatment Time Frame (Dates): January 1988- December 1990

Treatment:
Anatomic radical retropubic prostatectomy and pelvic lymphadenectomy

Patient Profile
Matched for Gleason score and clinical stage to Ragde *et al.* 1997
Gleason score 2-6
Clinically localized (stage T1 and T2)
38 of 287 men treated has a Gleason of 4 or less, so were included in study regardless of clinical stage or PSA level. In Ragde series 50 % of men had Gleason of 4 or less, so total of 76 men selected. The additional 38 men had a Gleason score of 5 or 6, clinical stage T2a/T2b. No selection made based on preoperative PSA, pathologic stage, length of follow-up, or clinical outcome.

When PSA used as a to match Ragde, didn't significantly change results.

There was a greater percentage of men in surgical series with PSA 0-4ng/mL, and a smaller percentage with PSA > 10ng/mL than in Ragde series

Study Design: retrospective

Results:
7-y actuarial PSA progression-free survival following RP was 97.8% (95% confidence interval) brachytherapy was 79% (95% confidence interval)

Complications: N/A

Comments:
Because Gleason score has been shown to be the single most predictive preoperative variable for biochemical progression following surgery, the Gleason score on the prostate biopsy was used for primary selection and matching of surgically treated men to brachytherapy-treated men

Biochemical progression-free survival following anatomic radical prostatectomy may be superior to 125I interstitial brachytherapy in patients with clinically localized disease.

Limitations: nonrandomized, inability to perform a valid statistical comparison because of the lack of the complete 125I data set, and patient selection bias.

Ragde et al. 1998 (35)

Ten-Year Disease Free Survival after Transperineal sonograpy-guided Iodine-125 Brachytherapy with or without 45-Gray External beam Irradiation in the Treatment of Patients with clinically Localized, low to high gleason grade prostate carcinoma.

 # Patients: 52 consecutive patients
5 patients lost to follow up, leaving 147 patients

Outcome Measurement Definition: Biochemical failure defined - PSA>0.5ng/mL. Clinical recurrence included a positive biopsy, radiographic evidence of metastases, or both. Treatment failure included positive bone scan, and/or positive biopsy, and/or PSA>0.5ng/mL

Follow-up Time (median): 119 months (3-134)

Patient Age (median): 70 years (53-92)

Treatment Time Frame (Dates): January 1987-June 1988

Treatment:
98 (64%) received Iodine125 brachytherapy alone – Group1- 160 Gy

54 (36%) also received 45 gray of external beam irradiation – judged to have a higher risk of extraprostatic extension. Group2
45Gy, 25 fractions of 1.8Gy each. Implant performed 2 weeks after completion of the external beam irradiation course. + 120 Gy implant
no androgen ablation

Patient Profile
T1-T3, low to high gleason grade prostate carcinoma
Pretreatment PSA ranged from 0.4-138ng/mL, with an average value of 11.0 ng/mL
Gleason grade median 5 (range 2-10)

Study Design: Retrospective
Non-randomized
No control

Results:
Overall survival 10 years after treatment was 65% including the brachytherapy alone group, and the brachytherapy + EBRT
Disease specific survival 98% (149/152)

5 y Disease free survival of group1 71% (68/96)
5 y Disease free survival of group2 80% (41/51)
combined is 74%

10 y disease free (PSA) survival group 1 60%
10 y disease free (PSA) survival group 2 76%
combined 66%

PSA failure, >0.5ng/mL, 29% if iPSA $\leq$10ng/mL, 40% if iPSA >10ng/mL
Biopsy failure, 23 patients, 15% of total population.
Post-treatment biopsy not available for 44 (29%).
Thus 22.3% of those biopsied were positive.

9 patients developed bone metastases (all had positive biopsies).
At last follow-up only 3 of 152 patients (2%) had died of prostate cancer.

Complications: N/A

Comments:
Group 2 had less favourable prognostic indicators, and yet with combined brachytherapy and EBRT, faired better than brachytherapy alone at 10 years.

Patients treated in different years than Ragde et al., 1997.

Stokes et al. 1997 (41)

Transperineal ultrasound-guided radioactive seed implantation for organ-confined carcinoma of the prostate.

 # Patients: 142

Outcome Measurement Definition: Evidence of local progression on DRE, 2 consecutive increases in the PSA level

Follow-up Time (median): 30 months (1-6 years)

Patient Age (median): mean 74 years (55-91)

Treatment Time Frame (Dates): October 1988-December 1992

Treatment:
Ultrasound-guided radioactive 125I seed implantation
16.8-52.52mCi (mean 33.67)

Patient Profile

Organ confined adenocarcinoma of the prostate
Gleason score ≤7
Well to moderately well differentiated tumour
Tumour clinically confined to the prostate
PSA≤50ng/mL, mean 10.6ng/mL

Study Design: retrospective

Results:
16.9% - (24/142) patients have recurrent or persistent cancer.
2.8% (4) have local prostate recurrence confirmed by biopsy.
2.8%(4) have metastatic bone disease
11% (16) have an increasing PSA without demonstrable clinical tumor, negative prostate biopsy, and scans, and are considered to have occult systemic metastasis.
4 patients died of metastatic cancer
Overall disease free survival at 2 years is 90%, and at 5 years is 76%.

Complications:
Transient radiation urethritis several weeks following procedure, typical
Grade 2 morbidity 19%
≥grade 3 4% - these numbers are after reducing dose to the periurethral area.
one patient experienced a fatal pulmonary embolus 2 weeks post-implant, which may have been unrelated to his implant.
1 patient required a diverting colostomy to alleviate painful proctitis.

Comments:
97% local control in the prostate and 76% NED survival is comparable to series using EBRT without the inconvenience of a protracted course of outpatient radiation therapy. In this era of managed care, seed implantation is an attractive alternative for early carcinoma of the prostate.

Nori & Moni 1997 (30)

Current Issues in Techniques of Prostate Brachytherapy

 # Patients: 47

Outcome Measurement Definition: Failure if rising PSA >1ng/mL

Follow-up Time (median): 37 months

Patient Age (median): 67 years (53-86)

Treatment Time Frame (Dates): 1990-1995

Treatment:
6 patients implanted with 103Pd
remainder with 125 I

Patient Profile
Median iPSA 11.3 ng/mL (1.5-100)
Stage T2a

Study Design: Retrospective

Results:
Local recurrence in 5/46 patients (11%)
Isolated biochemical failure in 8/46 (17%)
Actuarial clinical freedom-from-relapse was 79% at 5 years
Actuarial biochemical FFR 64% at 5 years

Complications:
Grade 3 urinary complications in 2/46 (4%)
No grade 4 urinary complications
No grade 3 or 4 rectal complications
Erectile function preserved in 32 (86%) of the 37 patients who were sexually active prior to treatment.

Comments:
Authors recommend brachytherapy for good risk patients, and a combination of EBRT and brachytherapy for intermediate risk group.

Grado et al. 1998 (16)

Actuarial disease-free survival after prostate cancer brachytherapy using interactive techniques with biplane ultrasound and fluoroscopic guidance.

 # Patients: 490 / 567potential brachytherapy patients. 24 judged to be ineligible, 53 had prior EBRT or brachytherapy and results are reported elsewhere.

Outcome Measurement Definition: Biochemical failure: 2 successive rising PSA values above the post-treatment PSA nadir value. In patients who underwent peri-treatment neoadjuvant androgen deprivation to shrink their tumors, biochemical failure was based on a rise in PSA above 1 ng/mL.

Failures scored as local, regional, distant, or unknown in origin.

Kaplan-Meier used for actuarial disease-free survival rates.

Follow-up Time (median): 46.9 months (22.1-94.6)

Patient Age (median):
no prior androgen deprivation brachytherapy: 70.4 (48.8-85.1)
+ EBRT 70.2 (50.2-88.8)

prior androgen deprivation brachytherapy: 67.5 (52.1-84.7)
+EBRT: 67.9 (52.6-72.4)

Treatment Time Frame (Dates): February 1990 – February 1996

Treatment:
Treatment planning performed using TRUS to determine prostate volume and seed implantation pattern.

Biplane ultrasound and fluoroscopic guidance.
381/490 patients received 103 Pd (78%) median 120 Gy
109/490 received 125I (22%) median 160 Gy
Post treatment CT scans performed to evaluate implant quality

Mean EBRT dose 45 Gy, administered in a median of 25 fractions over a mean of 34 d

Patients with no evidence of capsular extension or invasion were treated by brachytherapy alone. If there was evidence of possible capsular involvement, adjunctive EBRT was administered in addition to brachytherapy. 72 received adjunctive EBRT.

Patient Profile
36 patients had received prior androgen deprivation therapy (7%)

Among 454 patients without androgen therapy, pre treatment PSA median 7.5ng/mL (0.1-117.2)
Disease stage ranged from T1 to T3c, largest proportion T2a (32%) or T2b (50%)

Tumour grade moderately differentiated in 54%
Well differentiated in 23%
Poorly differentiated in 23 %

Study Design: retrospective

Results:
Actuarial disease free survival at 5-y was 79%
5-y actuarial rate of local control was 98%

No prior androgen deprivation brachytherapy: 80%
Brachytherapy + EBRT 72%

Prior androgen deprivation brachytherapy: 83%
Brachytherapy + EBRT 88%

No statistical difference between brachytherapy and brachytherapy + EBRT

local treatment failure in 5 patients
regional failure in 3
distant failure in 33
failure of unknown origin in 5
3 patients experienced both local and distant failure

Complications:
Acute urinary symptoms such as frequency, urgency, and nocturia common during the first 3 mo. following brachytherapy.
5 patients (1%) developed rectal fistula
gross hematuria observed in 2 (0.4%) of patients
significant post treatment pain in the form of penile dysuria in 4 (0.8%) and proctitis in 2 (0.4%)

Comments:
No absolute numbers for PSA failure are given. Results for overall survival given in actuarial percentages.

Rates of survival in the brachytherapy alone vs. brachytherapy + EBRT groups not significantly different, even though the EBRT group had more advanced disease.

103Pd delivers a higher initial radiation dose rate than 125I, and it has been suggested that 103Pd provides a theoretical advantage in eradicating rapidly dividing tumor cells. In the present study, isotope choice was not based upon tumour grade, and no significant difference could be demonstrated between the recipients of the two isotopes, even when tumor grade was taken into account.

Stone and Stock (43)

Prostate Brachytherapy: Treatment Strategies

 # Patients: 109 patients at low risk
152 at moderate risk
40 at high risk
= 301

Outcome Measurement Definition: PSA increase on 2 consecutive determinations above 1 ng/mL, or evidence of local recurrence on digital rectal examination, transrectal ultrasound, or biopsy.

Follow-up Time (median): Low risk: 18 months (1-7 years)
Moderate risk: 27 months (12-74)
High risk: 13 months (6-42 months)

Patient Age (median): N/A

Treatment Time Frame (Dates): N/A

Treatment:
Low risk treated with 125 iodine alone.

Moderate risk treated with 125 iodine or 103 palladium alone, or combined brachytherapy with 5 months of hormonal therapy

High risk were treated with combination brachytherapy, external beam irradiation and 9 months of hormonal therapy

Patient Profile
Low risk: PSA 10 ng/mL or less, Gleason score 6 or less, and clinical stage T2a or less
PSA ranged from 1.3 – 10 ng/mL (median 6.4), a third of the patients had Gleason scores 2-4, and an equal number had T1c and T2a lesions.
Moderate risk: PSA greater than 10ng/mL, Gleason score greater than 6, or stage T2b or greater. 68.3%had a PSA greater than 10 ng/mL, 50.6% had a Gleason score 7 or greater, and 64.5% had T2b or T2c stage.
High risk: PSA greater than 15 ng/mL, Gleason 8 or greater, clinical stage T2c to T3 or positive seminal vesicle biopsy (20). PSA ranged from 2.1 to 202 ng/mL (median 20), 32 had Gleason score 7 or greater (80%), and 34 had clinical stage T2b or greater (85%).

Study Design: Probably retrospective
Treatment based on presentation prognostic details

Results:
Low risk: Four year freedom from PSA failure rate was 91%.
Moderate risk: 4 year biochemical freedom from failure rate for the hormone group was 85% versus 58% for the no hormone group
High risk: the 3-year biochemical freedom from failure rate was 71%.

Prostate biopsies negative in 87% of low risk, 96.8 (hormone) and 68.6% (non hormone) of the moderate group, and 86% of high risk patients.

Complications:
Low risk: no patients experienced urinary incontinence. 4.5% of men experienced grade 1-2 radiation proctitis, and there were no cases of grade 3-4 radiation proctitis.
Moderate risk: Grade 1 to 2 radiation proctitis occurred in 1 patient receiving hormonal therapy (1.3%) and in 3 treated only with brachytherapy (4%). There were no cases of grade 3 or 4 radiation proctitis and no cases of urinary incontinence.

High risk: All 5 patients who received 5920 cGy external beam dose had gastrointestinal complications. There were no grade 3 or 4 gastrointestinal complications. The actuarial freedom from grade 2 proctitis was 82%. No patient experienced urinary incontinence.

Comments
The progression-free results in these low risk patients treated with 125I alone also compare favorably to what has been reported for similar groups of patients treated with radical prostatectomy or external beam irradiation.

The data also suggest inferior results compared to patients with low risk disease. Brachytherapy can be accomplished with low morbidity.

Critz et al. 1998 (8)

Simultaneous radiotherapy for prostate cancer: 125I Prostate implant followed by external-beam radiation.

 # Patients: 1020

Outcome Measurement Definition: Achieving and maintaining a post-treatment prostate-specific antigen of ≤0.5ng/mL. Failure is a nadir above 0.5 ng/mL, or PSA that subsequently rose above this level.

Follow-up Time (median): 3 years (1-14 years)

Patient Age (median): 67 (45-84) years

Treatment Time Frame (Dates): January 1984-December 1996

Treatment:
Radioactive 125I prostate implantation followed by external-beam irradiation
No hormone treatment

Retropubic implantation performed on 363 men, median dose 9000 cGy.
Ultrasound-guided transperineal 125I implant performed on 657 men, median dose 12000 cGy

Three weeks after either implant technique, external beam radiation was delivered at a daily dose rate of 150 cGy, for a total of 4500 cGy.

Combination bilateral 120 degree arc and conformal beam technique was employed

120 men, primarily those with high PSA or Gleason score, who were implanted by the transperineal technique, had a 750cGy external beam radiation boost to the implanted seminal vesicles.

Patient Profile
Median pretreatment PSA 7.5ng/mL (0.2-188ng/mL)

T1T2N0

Well differentiated carcinoma 27%

Moderately differentiated 54%

Poorly differentiated 19%

Study Design: Retrospective

Results:
Actuarial overall 5 year disease free (PSA) survival 79%

Actuarial overall 10 year disease free (PSA) survival 72%

At 5 years, significantly better disease free survival documented with ultrasound techniques (92%) vs. retropubic implant (73%)

Median time to recurrence 3.5 years (0-8.5 years)

No biopsies reported

Complications*:* N/A

Comments*:*
Implantation performed by both retropubic and transperineal techniques

Zeitlin et al., 1998 (54)

High dose combination radiotherapy for the treatment of localized prostate cancer

Patients*:* 212

Outcome Measurement Definition*:* Inability to achieve a PSA nadir of 0.5 ng/mL
Biochemical failure: failure to reach the nadir, or an absolute rise in PSA to 1 ng/mL in a patient with a prior nadir value. If the increase was less than 0.5 ng/mL, then 2 consecutive rises were required to declare a biochemical failure.

Follow-up Time (median): Mean 33 months (24-60)

Patient Age (median): Mean 67 (49-83)

Treatment Time Frame (Dates): January 1991- November 1996

Treatment:
Transperineal radioactive seed implantation followed by 45 Gy. EBRT

Isotope choice was based upon Gleason score and deoxyribonucleic acid ploidy.

Gleason score 2-5 treated with minimum peripheral dose of 120 Gy 125I

Gleason score 7-10 minimum peripheral dose 90 Gy of 103 palladium

All patients then received 45 Gy EBRT 4-6 weeks after seed implantation for 5 weeks in 25 equal fractions.

Conformal computerized preplanning dosimetry was done

Transrectal ultrasound was performed

Patient Profile

Clinically localized prostate cancer (T1-T3)

Study Design: Single institution treatment program

Results:
152/212 (72%) achieved a nadir of 0.5 ng/mL or less
Positive biopsies detected in 13.9% (20/144)

Estimated probability of *initial* biochemical success at 60 months 91%

Actuarial disease free survivor rate 72% when iPSA >20ng/mL
Actuarial disease free survivor rate 95% when iPSA ≤20ng/mL

Complications:
Proctitis in 21.4%
Impotence in 38%
Urinary retention in 1.5%
Incontinence in 2.8%
Rectoprostate fistula in 2.4%
Rectal wall breakdown in 0.5%
Urethral stricture in 0.5%
6 patients (2.8%) required colostomy and urinary diversion

Comments:
Brachytherapy plus external beam therapy

Levels of incontinence and impotence in this series comparable to other series for radiation or surgery., but higher than 3D conformal

Authors suggest positive biopsy does not preclude successful treatment – due to protracted course of radiation damage, 3 years may be better time to do biopsy, instead of 18 months to 24 months.

Mate et al. 1998 (28)

High Dose-Rate Afterloading 192Iridium prostate brachytherapy: feasibility report.

 # Patients: 103

Outcome Measurement Definition: PSA rising on 3 consecutive serial measurements. Time of failure is first rising.

Follow-up Time (median): 45 months (10-89 months)

Patient Age (median): 68.6 (48-78 years)

Treatment Time Frame (Dates): October 89- August 95

Treatment:
Multifractionated HDR-Ir192 and external beam
Treatment initiated with perineal needle placement using ultrasound guidance.
A postoperative CT scan was obtained to provide the basis for treatment planning.
Four HDR-Ir192 treatments given over a 40 hr period.
Minimal peripheral dose ranging from 3.0 to 4.0 Gy per fraction.
Two weeks later external beam radiation was added using 28 fractions of 1.8 Gy daily to a dose of 50.40 Gy.

Patient Profile
Mean pre-treatment PSA was 12.9ng/mL (median 8.1) with 90% of patients being above 4.0.
Patients with prostate volumes up to 105cc were implanted.

Study Design: Pilot study

Results:
14.6% (15/103) biochemical failure, 7% of patients with initial PSA less than 10, 10% of patients with PSA 10-20, and 40% of patients >20ng/mL at last check up.

Kaplan Meier plot 84% of patients with initial PSA <20 will be free of progression at 5 years, while 50% of patients with PSA >20 were free of progression.

No biopsies

Complications:
No significant operative or perioperative complications were encountered.
Genitourinary: 7: minor urethral stricure, 2: marked uropathy, 1: hematuria
Gastrointestinal: 2: spotty rectal bleeding

Comments:
Temporary placement of seeds

Dinges et al. 1998 (13)

High-dose rate interstitial with external beam irradiation for localized prostate cancer – results of a prospective trial

 # Patients: 82/87 who had IMP and EB: other malignancies in the last 5 years, previous radiotherapy in the pelvic region, 3 patients lost during follow-up

Outcome Measurement Definition: Positive biopsy combined with PSA vale > 1.0 ng/mL

Follow-up Time (median): 24 months

Patient Age (median): 67 (49-78)

Treatment Time Frame (Dates): October 1992- December 1994

Treatment:
9 or 10 Gy/week interstitially using high dose rate 192 Iridium
External beam 45 Gy / 25 fractions (40 / 20)

Patient Profile
Excluded if they experienced other malignancies in the past 5 years, or if they had previous radiotherapy to the pelvis
All patients pathologically proven to be node-negative
PSA value ≥10ng/mL found in 64.6% (53/82) patients
Median pretreatment PSA 14.0 ng/mL

Study Design: Prospective
Combined interstitial with external beam radiotherapy

Results:
PSA value <1.0 ng/mL in 52.9% of patients at 2 years

Negative biopsies 12 and 24 months after therapy were observed in 69.8% (44/63), and 73.1% (38/52) patients respectively.

Based on definition of failure as positive biopsy combined with PSA of >1.0ng/mL, local tumour control rate was 79.5% at 2 years.

Complications:
Acute side effects not increased over EBRT alone.
Severe side effects were seen in 3 patients, rectourethral fistulae requiring colostomy

Comments:
Tumour control rate higher than would be on PSA alone.
Temporary placement of seeds

Stromberg et al. 1987 (6)

Conformal High Dose Rate Iridium-192 Boost Brachytherapy in Locally Advanced Prostate Cancer: superior prostate-specific antigen response compared with external beam treatment.

 # Patients: 58: EBRT with brachytherapy boost,
278: EBRT

Outcome Measurement Definition: PSA >1.5ng/mL and rising on two consecutive values

Follow-up Time (median): 43 months for EBRT (1-91 months)
26 months for EBRT + brachytherapy boost (3-51 months)

Patient Age (median): EBRT: 74 years (54-91)
EBRT + boost: 70 years (56-85)

Treatment Time Frame (Dates): EBRT + boost: November 1991 – November 1995
EBRT: January 1987 – December 1991

Treatment:
45.6 Gy pelvic external radiation and three high dose rate iridium-192 conformal boost implants of 5.5 to 6.5 Gy each
External beam radiation to prostate-only fields (median dose 66.6 Gy)

Patient Profile
Median pretreatment PSA for EBRT 14.3ng/mL, Gleason 6, T2b to T3c
EBRT + brachytherapy boost: 14.0ng/mL, Gleason 7, T2b to T3c
All patients without evidence of nodal or distant metastases

Study Design
Retrospective
Kaplan-Meier method used to calculate actuarial rates

Results:
3 year actuarial biochemical control rates were 85% versus 52% for the conformally and conventionally treated patients, respectively.

No biopsies

Complications: N/A

Comments:
Results show a significant improvement in the biochemical response rate with conformal boost brachytherapy and pelvic external radiation compared with conventional radiation alone.

Temporary implants

Borghede et al. 1997 (6)

Combined treatment with temporary short-term high dose rate Iridium-192 brachytherapy and external beam radiotherapy for irradiation of localized prostatic carcinoma

 # Patients: 50

Outcome Measurement Definition
DRE – absence of any suspicious nodule as judged by DRE
TRUS-guided biopsies – no evidence of carcinoma in post-treatment core biopsies
Complete chemical control – PSA level ≤1.0ng/mL
Partial chemical control – PSA >1.0≤2.0ng/mL
Progressive disease – PSA >2.0ng/mL

Follow-up Time (median): 45 months (18-92)

Patient Age (median): Mean 63 years (50-75)

Treatment Time Frame (Dates): July 1988-June 1994

Treatment:
EBRT (50 Gy) 2.5 weeks prior to and following 192 Iridium brachytherapy (2x10Gy). Two brachytherapy sessions two weeks apart.

Patient Profile
38 patients with stage T1-2
12 patients with stage T3
30patients PSA <10ng/mL
12 10-20ng/mL
8 > 20ng/mL

Study Design*:* Probably retrospective

Results:
Clinical and biopsy verified local control achieved in 48/50 (96%) patients.
Post-treatment PSA ≤1.0ng/mL was seen in 42 (84%) patients

>1.0≤2.0ng/mL 4 (8%) of patients
>2.0ng/mL 4 (8%) or patients

No patient has succumbed due to the prostatic carcinoma. Two of the patients died during the follow-up, both of metastatic cancer from a colon and a rectal carcinoma after treatment with their prostate cancer locally controlled.

Complications:
No serious bleeding or infections.
Acute: 4 patients had mild to moderate dysuria
4 patients had urinary frequency
no incontinence
40 patients had diarrhoea (5 mild, 35 moderate)

Late side effects: 2 had mild dysuria
1 had mild haematuria
3 had urinary frequency
13 had mild diarrhoea
4 had moderate diarrhoea
1 had mild proctitis
5 had erectile dysfunction (of 42 potent before treatment)

Comments:
Local control results and minimal toxicity are promising. Long term results are necessary before general use.

Temporary implants.

Paul et al. 1997 (31)

Iridium 192 high-dose-rate brachytherapy – a useful alternative therapy for localized prostate cancer?

 # Patients: 40

Outcome Measurement Definition
Prostatic biopsy at 18 months after therapy
PSA (70% of patients)

Follow-up Time (median): Mean 74 months (16-130)

Patient Age (median): Mean 72.1 years (55-78)

Treatment Time Frame (Dates): 1984-1995

Treatment:
2 sessions at weekly intervals of Iridium 192 afterloading brachytherapy (9Gy)
+ 18X2 Gy EBRT 14 days later.
Hyperthermia is used for 30 minutes immediately following Ir192 placement.

Patient Profile
Not eligible for radical prostatectomy, because of either tumour stage (T3), , their age (>73) years, the presence of concurrent disease, contraindication for anesthesia, or because patient requested this therapy.
Pretreatment PSA mean 40.7 ng/mL, median 11.3ng/mL(0.5-406ng/mL)
5T1 tumours, 18T2, and 17T3

Study Design*:* Retrospective

Results:
35/40 patients remain alive. 2 died of myocardial infarction at 1 and 2 years after treatment, and another patient died at 1 year after therapy due to another unknown metastasizing tumor. One patient who developed a rectovesical fistula and severe proctitis after treatment died 7 months later due to renal insufficiency, severe generalized angiopathy, and consequent cerebral ischemic disease. One patient died of progressive disease.

Of 35 surviving patients, 7 suffered from clinical progression of disease (20.5%). Of these 7, 5 presented with elevated PSA values before clinical progression; the other 2 patients showed no

prior PSA elevation. 4 of these 7 patients had a positive biopsy 18 months after treatment, whereas 3 patients were negative on biopsy at that time.

32/40 patients had biopsies at 18 months, 21 showed no evidence of disease, 11 (34%) had a positive biopsy. (~70% clinical control at 18 months)

20% of treated patients showed signs of clinical progression after a mean follow-up period of more than 6 years.

At 18 months following treatment mean PSA value was 6.0 ng/mL (0.5-48), and the median was 1.1ng/mL. All but one patient showed a drop in PSA levels.

Complications:
Of the 17 patients potent prior to treatment, 4 reported erectile impotence after radiotherapy. (23.5%)
One rectovesical fistula (2.5%)
2 cases of necrosis of the prostate after therapy (5.0%)
4 acute cases of proctitis (10%)
4 acute cases of urethritis (10%)
32 acute cases of gross hematuria (80%)

Comments:
Results compare favourably with the rates of disease-free survival observed at 5 years, which range from 40-90% following different techniques of radiotherapy for localized prostate cancer as reported in the literature.

The rate of positive biopsy increases with higher tumour stage at diagnosis, therefore tumour control obtained in locally advanced disease by this method is insufficient.

Temporary implant

Teh et al. 1998 (47)

Permanent Gold-198 Implant for Locally Recurrent Adenocarcinoma of the Prostate after Failing Initial Radiotherapy.

 # Patients: 30

Outcome Measurement Definition: PSA less than 1 ng/mL, no increasing PSA level on 3 consecutive measurements, and no metastatic disease.

Follow-up Time (median): 54 months (12-79)

Patient Age (median): 67 years (54-80)

Treatment Time Frame (Dates): June 1990-January 1996

Treatment:
Salvage
Permanent transperineal 198-Au implant
Mean dose 20 Gy.
Mean activity 64.8 mCi.
TRUS, fluoroscopic and DRE guidance
Planning CT scan performed

Patient Profile
Locally recurrent prostate cancer after failing initial combined brachytherapy and EBRT
Gleason score 5-10

Study Design: retrospective

Results:
5/30 patients showed control of disease progression.
25 patients had rising PSA on at least 3 consecutive measurements
7 patients had bony metastases
1 patient had both bony and nodal metastases

Complications:
Acute GU, 7/30 patients experienced grade 1

4/30 patients experienced grade 2
Acute GI, 3/30 patients experienced grade 1
1/30 patients experienced grade 2
Late GU, 2/ 30 patients experienced grade 2
Late GI 1/30 patients experienced grade 2

Comments:
Brachytherapy with permanent 198Au seeds is a feasible option in a selected group of patients with locally recurrent prostate cancer and a low level of PSA. Re-implant with 198Au seeds can be performed with acceptable morbidity.

Grado et al. 1999 (15)

Salvage brachytherapy for localized prostate cancer after radiotherapy failure.

 # Patients: 49 patients

Outcome Measurement Definition
Outcome: disease status, PSA levels, treatment-related symptoms and complications
PSA failure: two successive risings after the post treatment nadir. Time to failure for biochemical relapses was calculated from the date of salvage treatment to the date of the first detectable rising PSA level after the post treatment PSA nadir.
Failure scored as local, distant, or unknown in origin.
Actuarial survival rates were determined by the Meier-Kaplan method

Follow-up Time (median): 64.1 months (26.6-96.8 months)

Patient Age (median): 73.3 years (52.9-86.9)

Treatment Time Frame (Dates): February 1990-March 1996

Treatment:
I125 or Pd103
Transperineal percutaneous implantation
Fluoroscopic and biplane ultrasound guidance.
37 (76%) implanted with Pd
12 (24%) implanted with I125
4 patients received adjunctive EBRT, median dose 45 Gy, administered in a median of 25 fractions, over a median of 33 days.
8 patients (16%) received neoadjuvant hormone therapy before brachytherapy

Patient Profile:
Pretreatment PSA level median 5.6 ng/mL (1.5-79.1)
46/49 had EBRT, and 3 had brachytherapy previously
median elapsed time between primary therapy and salvage therapy was 41.7 months (21.8-185.2)
Grade at time of salvage brachytherapy
Well differentiated 10%
Moderately differentiated 35%
Poorly differentiated 55%

Study Design: Retrospective

Results:
Local failure occurred in 1 patient, and distant failure in 26. 1 patient with local failure also experienced distant failure
Rate of clinical local control for all patients was 98%
Overall survival at 3 and 5 years was 75% and 56 % respectively.
Disease specific survival at 3 and 5 years was 89% and 79% respectively
Biochemical disease free survival actuarial at 3 and 5 years was 48% and 34% respectively.

Complications:
60% patients reported they were sexually inactive before treatment
one patient reported decreased capacity for sexual activity after salvage brachytherapy

Acute urinary symptoms such as frequency, urgency, hesitancy, and nocturia common during the first 3 months after brachytherapy
7 patients (14%) received post treatment TURP 95 had had previous TURP)
2 patients (4%) experienced persistent gross hematuria
Significant post treatment pain in the form of penile dsysuria in 3 (6%) of patients
2 patients (4%) developed rectal ulcers
1 patients (2%) underwent colostomy for rectal bleeding
Incontinence developed in 3 patients (6%) after undergoing TURP

Comments:
Locally recurrent prostate adenocarcinoma after radiotherapy failure has been reported to be associated with significantly higher histologic grades than those at original diagnosis.

Appendix D: Levels of Scientific Evidence

Level Highest (I) to Lowest (IX)	Strength of evidence	Type of study design	Conditions of scientific rigour*
I	Good	Meta-analysis of randomized controlled trials	Analysis of patient individual data Meta-regression Different techniques of analysis Absence of heterogeneity Quality of studies
II		Large sample randomized controlled trials	Assessment of statistical power Multicentre Quality of the study
III	Good to Fair	Small sample randomized controlled trials	Assessment of statistical power Quality of the study
IV		Non-randomized controlled prospective studies	Concurrent controls Multicentre Quality of the study
V	Fair	Non-randomized controlled retrospective trials	Historical controls Quality of the study
VI		Cohort studies	Concurrent controls Multicentre Quality of the study
VII		Case-control studies	Multicentre studies Quality of the study
VIII	Poor	Non-controlled clinical series Descriptive studies: surveillance of disease, surveys, registers, data bases, prevalence studies Expert committees, consensus conferences	Multicentre
IX		Anecdotes or case reports	

*Quality of study assessed by specific protocols and conditions of scientific rigour.

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