Prostate Cancer and Prostatic Diseases (2004) 7, 201–207
 1365-7852/04 $30.00
www.nature.com/pcan

Review

Iodine seed prostate brachytherapy: an alternative first-line choice for early prostate cancer

SEM Langley[1]* & RW Laing[2]

[1]*Department of Urology, St Luke's Cancer Centre, Royal Surrey County Hospital, Guildford, UK; and* [2]*Department of Oncology, St Luke's Cancer Centre, Royal Surrey County Hospital, Guildford, UK*

This article on permanent iodine-125 seed prostate brachytherapy reviews the techniques, results, and patient selection issues for early prostate cancer. The long-term 10 y results of brachytherapy from Seattle, and their reproducibility in other centres both in the USA and UK are reported. The use of hormone therapy in brachytherapy and the value of combining external beam radiotherapy with a brachytherapy implant are discussed. Reviewed comparative data show the similarity of biochemical survival in patients treated with brachytherapy, radical prostatectomy, and external beam radiotherapy. The role of brachytherapy as a first-line treatment option for patients with prostate cancer is demonstrated.
Prostate Cancer and Prostatic Diseases (2004) **7,** 201–207. doi:10.1038/sj.pcan.4500727
Published online 8 June 2004

Keywords: iodine seed; prostate; brachytherapy; cancer

Introduction

Modern day prostate brachytherapy using permanent implants was born in the 1980 s following the development of transrectal ultrasound in Denmark.[1] The use of transrectal ultrasound (Figure 1) allows the accurate implantation of radioactive seeds into the prostate that had previously been attempted at open operation but without clinical success.[2]

Brachytherapy procedure

There are a number of different techniques available to perform prostate brachytherapy, all of which, when performed by experienced hands, provide reproducible high-dose radiation targetted to the prostate (minimum 145 Gy with iodine-125). There does not appear to be any clinical difference between the isotopes of iodine-125 and palladium 103,[3,4] and the latter is currently unavailable for routine use in the UK and much of Europe. The implant procedure as popularised in Seattle is a two-stage technique involving an initial planning transrectal ultrasound scan.[5] The ultrasound images generated of the prostate are digitised to produce a three-dimensional computerised model of the prostate, urethra and rectum. The precise number and position of the seeds required are then calculated to ensure coverage of the prostate with a suitable margin. Seed arrangement commonly used is termed 'modified peripheral loading'. In this technique seeds are placed evenly throughout one 5 mm slice alternating with peripheral placement at the next 5 mm cut. The seeds are calibrated and preloaded into the needles prior to the implant. The patient returns to the hospital 2–4 weeks later for the implantation of the radioactive sources. Some centres utilise real-time planning where the planning and treatment occur during the same theatre session. In this method, the procedure takes longer but benefits from the fact that patients do not need to be repositioned between planning and treatment.

The procedure is carried out under general or spinal anaesthesia, the patient is placed in a similar extended lithotomy position as for the planning scan. Transrectal

*Correspondence: SEM Langley, Department of Urology, St Luke's Cancer Centre, Royal Surrey County Hospital, Guildford GU2 5XX, UK.
E-mail: stephen.langley@dial.pipex.com
Received 22 January 2004; revised 29 March 2004; accepted 7 April 2004; published online 8 June 2004

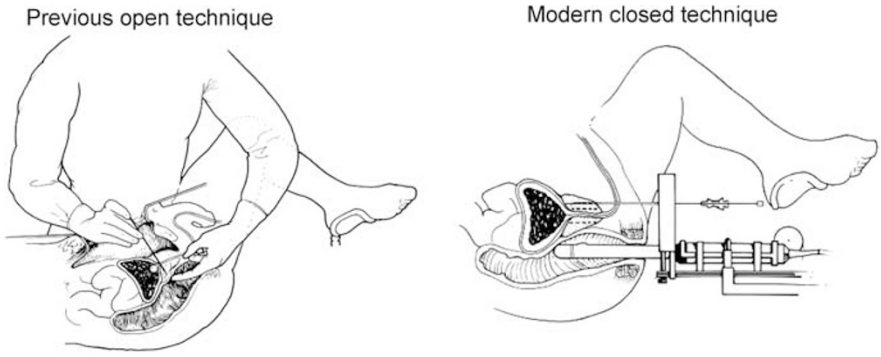

Figure 1 *Comparison of the previous and modern day techniques of prostate brachytherapy.*

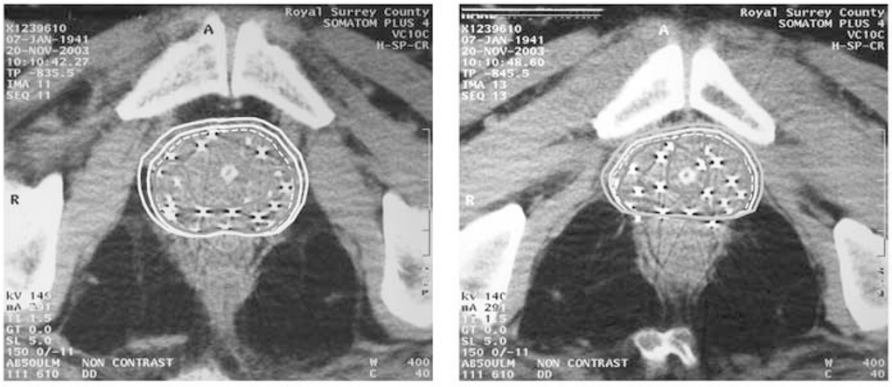

Figure 2 *Postimplant CT scan taken with the patient catheterised at mid gland and apical levels of the prostate The Iodine-125 sources are clearly seen within the prostate tissue The dashed white line shows the periphery of the prostate The green isodose line is a simulation showing coverage of the prescribed radiation dose, 145 Gy. The red isodose line simulates that portion of the prostate receiving 150% of the prescription dose, 217 Gy. The blue isodoseline simulates the 72 Gy isodose showing the rapid fall off in radiation to the surrounding structures.*

ultrasound is used to guide the needles, preloaded with radioactive seeds, into their predetermined positions within the prostate gland. The procedure takes 30–45 min after which the patient is catheterised. The catheter may then be removed later the same day with the patient being discharged once they have voided or the following day.

Postoperative CT scans are performed at either day one or 1 month from the implant to assess the quality of each implant. This allows any systematic errors to be identified by the team and any individual's poor implant can be corrected. This is in contrast to the early days of brachytherapy when dose distribution was poor and there was little quality control of the freehand technique.

The minimum prescribed dose to the prostate gland is 145 Gy using Iodine-125 implants with approximately 50% of the gland receiving 150% of the dose, that is, 217 Gy, see Figure 2. The implants are arranged to allow relative sparing of the prostatic urethra to minimise urinary morbidity. Stranded Iodine seeds (Rapid Strand™, Oncura, UK) allow a greater coverage of radiation just outside the gland and the risk of individual seed migration through the venous plexus around the prostate is avoided. In our audit of 40 patients who underwent a chest X-ray a minimum of 3 months after their Rapid Strand™ implant there were no cases of seed migration to the lungs. Implants are typically planned with a minimum margin of 5 mm around the prostate, extending to 10 mm at the base and apex in an attempt to treat any localised extracapsular spread of disease.

In cases where there is an increased chance of local extension of the prostate cancer, a combination treatment using 45 Gy external beam radiation to the pelvis, given as 1.8 Gy/fraction, combined with a 110 Gy brachytherapy implant has been used to good effect and will be discussed below. In some series the addition of 3 months neoadjuvant hormone therapy is also being utilised.

Brachytherapy results

Long-term results

The first 10 y results of transperineal ultrasound-guided prostate brachytherapy that were derived from Seattle were reported in 1998.[6] The 152 patients treated from 1986 to 1987 were the first ever to be treated by this technique and therefore include both the learning curve as well as the curve of discovery for the procedure. In all, 64% of patients were treated by implant alone (either Iodine 125 or Palladium-103) and the remaining 36% of patients judged to be at higher risk of extraprostatic extension underwent combined EBRT to 45 Gy followed by brachytherapy. Five and 10 y PSA biochemical-free

survival as defined with a PSA of $<0.5\,\mu g/l$ revealed results of 74 and 66%. This learning curve was demonstrated in a more contemporary series of similar low-risk patients (defined in Table 1) treated in Seattle from 1988 to 1999. Improvements in the technique revealed an increased 10 y biochemical-free survival rate from 65 to 87% for this group of patients.[7]

A further cohort of 125 patients treated by Iodine-125 monotherapy, with an average follow-up of 77 months revealed 100% cancer specific survival and an 85% progression-free survival at 10 y.[7,8] The overall Seattle published series of 634 patients, 402 treated with an implant alone (Iodine 125/Palladium-103), and 232 treated by an implant and external beam radiation revealed a progression-free survival rate of 77%.[8,9] No patients underwent lymph node sampling or androgen ablation, and biochemical relapse-free survival was determined by two successive PSA rises rather than the more standard ASTRO criteria of three. When stratified by risk factors, see Table 1. low intermediate, and high-risk disease had progression-free survival rates of 87, 74, and 45%, respectively. Similar 10 y results have been recently reported by others with PSA relapse-free survival rates of 79% from a cohort of 883 patients[10] and results on 619 patients at 13 y continue to show a PSA-free survival of 77%.[11]

Table 1 Risk group classification of prostate cancer patients

Seattle risk groups	PSA	Stage	Gleason grade
Low	≤10	T1a–T2b	2–6
Intermediate: 1 factor	>10	≥T2c	≥7
High: 2 or more factors	>10	≥T2c	≥7

Stage is based on the 1992 American Joint Committee on Cancer staging where T2b involves more than 50% on one side of the gland and T2c involves both sides as assessed by DRE.

Reproducibility of brachytherapy results

Several centres across America have reported similar results for low-risk patients as indicated in Table 2.[12–16] For patients treated by brachytherapy monotherapy for intermediate-risk cancer the results in the literature are more varied. In series with demonstrable high-quality implants and who are regularly performing brachytherapy, excellent results have been seen with biochemical free survival of this group of patients matching those obtained from Seattle, Table 3.[6,13,17–22] In other series where the quality of the implant as determined by the postimplant dosimetry was unrecorded, or the data largely represented the learning curve of the institution, poor results have been reported and perhaps the addition of EBRT may have improved survival.

The results achieved in the USA appear exportable to the UK. Although it is early to report results from our series of over 400 patients, currently we have an actuarial biochemical-free survival of 93% from 272 patients whose follow-up ranges from 9 to 55 months, mean 29 months. The Leeds group. UK, have also recently presented their 7 y PSA-free survival results showing similar outcomes to those from America with rates of 84, 72 and 54% for low-, intermediate- and high-risk disease from a cohort of 669 patients.[23]

Table 2 PSA progression-free survival for patients with low-risk prostate cancer (iPSA ≤10, Gleason ≤6, stage ≤T2b) demonstrating the reproducibility of the results initially reported from the Seattle group

Series	Year	Patient numbers	Failure definition, PSA	Follow-up (y)	PSA progression free survival (%)
Potters[12]	1999	717	>1.0 & 3 rises	5	93
Zeleksky[13*]	2000	112	>1.0& 3 rises	5	88
Lederman[14]	2001	165	>1.0	5	88
Peschel[15]	2001	210	>1.0 & 2 rises	5	85
Stone[16]	2003	75	>1.0 & 2 rises	8	88

([*]CT guided I-125 brachytherapy).

Table 3 PSA progression-free survival for patients with intermediate-risk prostate cancer according to differing definitions

Series	Type of therapy	Intermediate group definition	Follow-up (y)	PSA progression free survival (%)
Unsatisfactory outcomes				
D'Amico[17]	Monotherapy	iPSA 10–20 and/or Gleason 7 and/or stage T2b	5	35
Ragde[6]	Monotherapy	iPSA ≥10 or Gleason ≥7 or stage ≥T2c	10	34
Kwok[19]	Monotherapy	iPSA ≥10 or Gleason ≥7 or stage ≥T2c	5	63
Brachman[22]	Monotherapy	iPSA 10–20, Gleason = 7 or stage ≤T2	5	28
Satisfactory outcomes				
Merrick[20]	Monotherapy	Gleason 7, stage ≤T3a	5	90
Potters[21]	Monotherapy	iPSA ≥10 or Gleason ≥7 or stage ≥T2c	5	79
Zelefsky[13]	Monotherapy	iPSA ≥10 or Gleason ≥7 or stage ≥T2c	5	77
Lee[18]	Monotherapy+hormonetherapy	Stage T1b–T3b & iPSA ≥10 or Gleason ≥7	4	94

Those results from centres reporting their initial learning curve experience or where CT postimplant dosimetry was not routinely performed to assess implant quality are separated from those centres regularly performing brachytherapy with demonstrated high-quality implants.

The benefit of treating patients with intermediate-risk factor disease by brachytherapy alone or in combination with external beam radiotherapy has yet to be clarified and there are proponents of each technique. Initially, there was agreement to treat patients with a Gleason score of 7, an iPSA $>10\,\mu g/l$ and/or an clinical stage of T2b or greater by combination therapy. However, with improved techniques and favourable outcomes of patients treated by monotherapy with high iPSA levels and Gleason scores the rationale is under question.[20,24] Furthermore, detailed pathological studies have shown that the radial extent of extraprostatic cancer extension is almost always ≤ 5 mm which should be within the confines of a monotherapy brachytherapy dose distribution.[25] A current RTOG study randomising intermediate-risk patients to brachytherapy alone or combination therapy should answer the question as to the necessity of external beam radiotherapy. One might imagine that where reproducibly high-quality implants can be performed, the increased risk benefit will be diminished with combination treatment.

The role of hormone therapy in brachytherapy

Hormone therapy may be used to reduce gland size to allow patients with larger prostates($\geq 60\,cm^3$) to be treated by brachytherapy without incurring pubic arch interference at the time of implantation. It has also been used in a neoadjuvant setting in higher risk patients in an analogous situation to patients treated by external beam radiotherapy. However, the excellent results demonstrated in patients treated with low-risk prostate cancer implies that neoadjuvant therapy in this group is unwarranted. When volume reduction is the goal, goserelin has been shown to provide a significantly greater reduction in prostate size than bicalutimide 150 mg, mean volume reduction 26 *vs* 8%, respectively.[26]

The value of neoadjuvant hormone therapy in a therapeutic role is more contentious. Following the work of Pilepich *et al*,[27] who demonstrated an improved survival of patients treated with 4 months combined androgen blockade with external beam radiotherapy, many patients in the UK are treated in a similar way when undergoing such therapy. Further studies have suggested that high-grade tumours require longer adjuvant treatment.[28] There are no randomised studies evaluating the benefit of neoadjuvant hormones with brachytherapy. To date some studies have shown an advantage for intermediate- and high-risk patients at 5 y,[18] where as others have failed to identify a benefit in case-matched series.[29,30] Furthermore, any such advantages must be balanced by the side effects of hormone therapy, which in our experience can adversely affect erectile function 1 y after implantation.

PSA bounce

A transient rise or bounce in the PSA, (usually $<3.0\,\mu g/l$) during follow-up is common occurring typically between 12 and 30 months postimplant in up to one-third of patients.[31–33] The cause of the rise is uncertain but multivariate analysis has shown a correlation with younger patients, high-dose implants and larger gland sizes.[32,33] There does not appear to be a correlation with the long-term biochemical outcome.[31,32]

Comparison results

There are currently no randomised studies comparing brachytherapy to either radical prostatectomy or external beam radiotherapy available. The SPIRIT study that had recently been launched in the UK to randomise patients with low-risk disease to either prostate brachytherapy or radical prostatectomy, has been abandoned due to recruitment difficulties in the larger US arm. There have therefore been attempts to try and determine whether brachytherapy is as effective as the other more conventional treatments and as a result a number of nonrandomised studies have been undertaken. A recent prospective study of over 6500 patients treated with either brachytherapy, radiotherapy or radical prostatectomy, who were stratified according to a PSA and Gleason score, would appear to show that there is no significant difference between any of the primary treatment options.[34] The only consistent finding was that conformal beam radiotherapy fared better than conventional external beam radiotherapy but no individual treatment had overall superiority. A further retrospective comparison of 1305 patients treated for stage T1-2 prostate cancer by either radical prostatectomy or brachytherapy failed to demonstrate any clear superiority of one treatment over the other.[35]

Kupelian reveals similar data from a large cohort of 2991 patients treated with either brachytherapy with or without external beam radiotherapy, conformal beam radiotherapy to >72 or 72 Gy and radical prostatectomy. External beam radiotherapy given to <72 Gy appeared less effective than the other modalities, all of which appeared indistinguishable assessed at 5 y by biochemical-free survival.[36]

It appears highly unlikely, given the size of these cohorts, that one will be able to determine a significant difference between treatment groups until randomised studies are available, and at present brachytherapy, radical prostatectomy and conformal beam radiotherapy would appear to hold similar chances of cure for patients. The durability of brachytherapy has been demonstrated in 10 and 13 y results from Seattle. No further recurrences were identified in patients who were deemed biochemically free at 10 y compared to 12[37] or 13 y of follow-up.[11] Only 25% of the recurrences occurred after 5 y of follow-up[37] a figure directly comparable to that following radical prostatectomy at Johns Hopkins Hospital. USA. where 23% of patients developed recurrence after 5 y of undetectable PSA measurements.[38]

Complications

Incontinence is rare, occurring in $<1\%$ in our work and most contemporary series. [39–42] The primary complication of prostate brachytherapy is a temporary deterioration of urinary function with increased irritative and

obstructive symptoms. Patients are routinely treated with α-blockers.[43] We have found that such urinary symptoms assessed by the IPSS are improved at 3 months and return to baseline by 9 months.[39] Indeed, patients at 2 and 3 y postimplant had lower IPS scores than their pretreatment levels. Urinary retention can occur in 2–27% of patients,[13,41,44] although with improved case selection the risk can be minimised. This side effect is best managed by intermittent self-catheterisation and is usually resolved within 4 weeks. A TURP should be avoided for at least 9 months as symptoms will often resolve and we have a $<2\%$ incidence of our patients requiring such surgery. Although urinary obstruction can often be readily relieved at operation, a 26% rate of stress incontinence has been reported.[45] Patients at risk of temporary urinary retention after brachytherapy include those urodynamically obstructed, with prostates $>35\,cm^3$, moderate to severe IPSS scores and postvoid residuals greater than $200\,cm^3$ pretreatment.[39]

Proctitis is relatively uncommon, occurring in approximately 5% of cases[46,47] and in our experience has always resolved with conservative medication alone. It is more troublesome in patients with combined EBRT and brachytherapy as the rectal dose is increased. Patient administered questionnaires have shown that there is relatively little long-term bowel dysfunction.[46] Pelvic pain and symptoms of prostatitis can occur but in our experience this is rare.

Erectile dysfunction seems significantly less common than with radical prostatectomy, where impotence from UK and European studies is as high as 86% despite utilising nerve sparing techniques.[48–50] Potters reported on the potency of 482 patients potent pretreatment and revealed a potency rate as high as 90% in men younger than 60 y and treated with an implant alone.[51] The potency rates gradually worsened with increasing age of the patient, the addition of external beam radiotherapy and the used of neoadjuvant androgen depravation therapy. In those patients that do experience impotence a $>80\%$ response to sildenafil can be expected.[52] Preimplant erectile status is a strong predictor of brachytherapy-induced impotence.[53] At 6 y postimplant, 70% of patients remained potent who enjoyed normal erectile function pretreatment compared to only 34% of patients whose pretreatment erectile function were sufficient for intercourse but considered suboptimal.[53] In our prospective study at Guildford, we have a 75% potency rate at 1.5 y in patients with IIEF score of greater than $\geq 11/25$, who were potent pretreatment. Potent patients may experience a dry ejaculate.

The literature lacks any randomised studies comparing side-effect profiles with external beam radiotherapy, radical prostatectomy or brachytherapy. The radical treatments available are themselves very different in nature and, where one individual will be naturally drawn to surgery through personal experiences, another may be keen to avoid an operation. A recent review article in the Lancet discussing the clinical decision-making aspects of the treatment of early prostate cancer, highlighted the relatively low risk of urinary incontinence, rectal complications and sexual dysfunction following brachytherapy compared to radical prostatectomy or external beam radiotherapy.[54] However, the risk of retention following brachytherapy is appreciable and highlights the importance of careful case selection to minimise this significant, although temporary deterioration in urinary symptoms. Quality-of-life studies suggest that the greatest deterioration in urinary continence and sexual function occurs in patients treated by radical prostatectomy compared to brachytherapy[55,56] although often more global quality of life measures remain similar.[50,57]

Patient selection issues for brachytherapy

Patient selection for prostate brachytherapy involves both cancer issues as well as more general urological issues. In accordance with the recommendations of the American Brachytherapy Society[58] and the EAU/EORTC,[57] patients with low-risk prostate cancers may be treated effectively with a brachytherapy implant alone. Those with intermediate-risk prostate cancer pose a more difficult question, and the current RTOG study randomising patients to a brachytherapy implant alone or combination treatment with EBRT will help to determine which is the optimal treatment strategy. Factors such as patient age, competing comorbidities, the percentage of cores positive for cancer[59] and the presence of perineural invasion can influence the decision as whether to currently offer combination treatment.

For patients with high-risk cancers, the role of brachytherapy is less certain. If there is evidence of seminal vesicle invasion, combination treatment of brachytherapy and EBRT does not provide as high a dose to the vesicles as conformal beam radiotherapy, which would be considered the optimum treatment. However, if the seminal vesicles appear clear, combination therapy has been used with good effect, as demonstrated in a number of series with up to 50% biochemical-free survival at 10 y.[9,24] Brachytherapy may be the treatment of choice in those patients who suffer from colitis or have had previous radiotherapy for testicular tumours due to the small volume of normal tissue irradiated.

The urological issues surrounding prostate brachytherapy are important in selecting patients who are likely to have minimal postimplant symptoms. Patients should ideally have glands less than $60\,cm^3$ in size to avoid pubic arch interference, although this can occur with smaller glands and needs to be assessed at the time of the planning scan. In patients whose glands are between 60 and $80\,cm^3$, a 3-month course of hormone deprivation via an LHRH analogue will usually allow sufficient volume reduction to permit an adequate implant.[26] Such patients however, tend to have an increased risk of temporary retention and urinary morbidity.[60] Patients must be able to flex their hips to 90°, have few pretreatment lower urinary tract symptoms, (IPSS <15) and should be urodynamically unobstructed.[39]

Prior TURP is a relative contraindication as the remaining defect in the prostate is difficult to adequately implant and such cases have been associated with increased morbidity. However, patients who have had a TURP/bladder neck incision many years prior to the diagnosis of prostate cancer, in whom there is no

appreciable intraprostatic defect, may be treated safely with an implant without the incontinence risk associated following a recent TURP.

Summary

Brachytherapy appears highly effective in the treatment of localised prostate cancer and these results have been reproduced across America as well as within Europe. A number of quality of life surveys have suggested that optimum quality of life is obtained with brachytherapy both in terms of urinary and sexual parameters. With many patients treated by brachytherapy in a day-case setting and being able to return to work within a few days, the advantages of brachytherapy are readily apparent. As with every treatment in medicine, however, case selection is critical in brachytherapy to ensure satisfied patients with a low morbidity and high chance with of cure.

The results presented here show that Prostate bracytherapy is now an established first-line treatment choice for low-risk disease. The results for intermediate risk compare favourably with the best published for other treatment modalities and brachytherapy should now be considered as an option for such suitable patients as well.[61]

References

1 Holm HH *et al*. Transperineal 125iodine seed implantation in prostatic cancer guided by transrectal ultrasonography. *J Urol* 1983; **130**: 283–286.
2 Zelefsky MJ, Whitmore Jr WF. Long-term results of retropubic permanent 125iodine implantation of the prostate for clinically localized prostatic cancer. *J Urol* 1997; **158**: 23–29, discussion 29–30.
3 Cha CM *et al*. Isotope selection for patients undergoing prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 1999; **45**: 391–395.
4 Wallner K *et al*. 1-125 *vs* Pd-103 for low-risk prostate cancer: morbidity outcomes from a prospective randomized multicenter trial. *Cancer J* 2002; **8**: 67–73.
5 Grimm PD, Blasko JC, Ragde H. Ultrasound-guided transperineal implantation of iodine-125 and palladium-103 in the treatment of early stage prostate cancer. Technical concepts in planning, operative technique and evaluation. *Urol Clin North Am* 1994; **2**: 113–125.
6 Ragde H *et al*. Ten-year disease free survival after transperineal sonography-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. *Cancer* 1998; **83**: 989–1001.
7 Grimm PD *et al*. 10-year biochemical (prostate-specific antigen) control of prostate cancer with (125)I brachytherapy. *Int J Radiat Oncol Biol Phys* 2001; **51**: 31–40.
8 Blasko JC *et al*. The role of external beam radiotherapy with I-125/Pd-103 brachytherapy for prostate carcinoma. *Radiother Oncol* 2000; **57**: 273–278.
9 Sylvester JE *et al*. Ten-year biochemical relapse-free survival after external beam radiation and brachytherapy for localized prostate cancer: the Seattle experience. *Int J Radiat Biol* 2003; **57**: 944–952.
10 Potters L *et al*. Importance of implant dosimetry for patients undergoing prostate brachytherapy. *Urology* 2003; **62**: 1073–1077.
11 Ragde H, Gardo GL, Nadir B. Brachytherapy for clinically localized prostate cancer: thirteen year disease-free survival of 769 consecutive prostate cancer patients with permanent implants alone. *Arch Esp Urol* 2001; **54**: 739–747.
12 Potters L *et al*. Risk profiles to predict PSA relapse-free survival for patients undergoing permanent prostate brachytherapy. *Cancer J Sci Am* 1999; **5**: 301–306.
13 Zelefsky MJ *et al*. Five-year biochemical outcome and toxicity with transperineal CT-planned permanent 1-125 prostate implantation for patients with localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2000; **47**: 1261–1266.
14 Lederman GS *et al*. Retrospective stratification of a consecutive cohort of prostate cancer patients treated with a combined regimen of external-beam radiotherapy and brachytherapy. *Int J Radiat Oncol Biol Phys* 2001; **49**: 1297–1303.
15 Peschel R, Han S, Colberg J. Ultrasound guided transperineal implant (IMP) *vs* radical prostatectomy for early prostate cancer. *Int J Radiat Biol* 2001; **51** (Suppl 1): 292.
16 Kollmeier M, Stock R, Stone N. Biochemical outcomes after prostate brachytherapy with 5-year minimal follow-up: improtance of patient selection and implant quality. *Int J Radiat Biol* 2003; **57**: 645–653.
17 D'Amico AV *et al*. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998; **280**: 969–974.
18 Lee LN, Stock RG, Stone NN. Role of hormonal therapy in the management of intermediate- to high-risk prostate cancer treated with permanent radioactive seed implantation. *Int J Radiat Oncol Biol Phys* 2002; **52**: 444–452.
19 Kwok Y *et al*. Risk group stratification in patients undergoing permanent (125)I prostate brachytherapy as monotherapy. *Int J Radiat Oncol Biol Phys* 2002; **53**: 588–594.
20 Merrick GS *et al*. Biochemical outcome for hormone-naive patients with Gleason score 3+4 *vs* 4+3 prostate cancer undergoing permanent prostate brachytherapy. *Urology* 2002; **60**: 98–103.
21 Potters L *et al*. A comprehensive and novel predictive modeling technique using detailed pathology factors in men with localized prostate carcinoma. *Cancer* 2002; **95**: 1451–1456.
22 Brachman DG *et al*. Failure-free survival following brachytherapy alone or external beam irradiation alone for T1-2 prostate tumors in 2222 patients: results from a single practice. *Int J Radiat Oncol Biol Phys* 2000; **48**: 111–117.
23 Bottomley DM, Ash D. *Prostate Brachytherapy Leeds 7 year results*, B.S.o. Oncology Birmingham 2003.
24 Blasko JC *et al*. Palladium-103 brachytherapy for prostate carcinoma. *Int J Radiat Oncol Biol Phys* 2000; **46**: 839–850.
25 Davis BJ *et al*. The radial distance of extraprostatic extension of prostate carcinoma: implications for prostate brachytherapy. *Cancer* 1999; **85**: 2630–2637.
26 Henderson A, Langley SEM, Laing R. Is bicalutamide equivalent to goserelin for prostate volume reduction before radiation therapy? A prospective observational study. *Clin Oncol* 2003; **15**: 318–321.
27 Pilepich MV, Winter K, John MJ. Phase III radiation therapyoncology group (RTOG) trial 86-10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced prostate cancer. *Int J Radiat Biol* 2001; **50**: 1243–1252.
28 Horwitz E *et al*. Subset analysis of RTOG 85-31 and 86-10 indicated an advantage for long-term *vs* short-term adjuvant hormones for patients with locally advanced nonmetastatic prostate cancer treated with radiation therapy. *Int J Radiat Biol* 2001; **49**: 947–956.
29 Sylvester J *et al*. Short-course androgen ablation combined with external-beam radiation therapy and low-dose-rate permanent brachytherapy in early-stage prostate cancer: a matched subset analysis. *Mol Urol* 2000; **4**: 155–159, discussion 161.
30 Potters L *et al*. Examining the role of neoadjuvant androgen deprivation in patients undergoing prostate brachytherapy. *J Clin Oncol* 2000; **18**: 1187–1192.
31 Wallner K, Blasko J, Dattoli M. *Prostate Brachytherapy made Complicated*, 2nd edn. SmartMedicine, Seattel 2002.

32 Merrick GS *et al*. Prostate-specific antigen spikes after permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2002; **54**: 450–456.
33 Stock RG, Stone NN, Cesaretti JA. Prostate-specific antigen bounce after prostate seed implantation for localized prostate cancer: descriptions and implications. *Int J Radiat Oncol Biol Phys* 2003; **56**: 448–453.
34 Vicini FA *et al*. An interinstitutional and interspecialty comparison of treatment outcome data for patients with prostate carcinoma based on predefined prognostic categories and minimum follow-up. *Cancer* 2002; **95**: 2126–2135.
35 Sharkey J *et al*. Brachytherapy *vs* radical prostatectomy in patients with clinically localized prostate cancer. *Curr Urol Rep* 2002; **3**: 250–257.
36 Kupelian PA *et al*. Radical prostatectomy, external beam radiotherapy <72 Gy, external beam radiotherapy >72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1–T2 prostate cancer. *Int J Radiat Oncol Biol Phys* 2002; **54**: 38 (61).
37 Ragde H *et al*. Modern prostate brachytherapy Prostate specific antigen results in 219 patients with up to 12 years of observed follow-up. *Cancer* 2000; **89**: 135–141.
38 Pound CR *et al*. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999; **281**: 1591–1597.
39 Henderson A *et al*. Toxicity and early biochemical outcomes from 125Iodine prostate brachytherapy in the UK. *Clin Oncol* 2004; **16**: 95–104.
40 Ragde H *et al*. Brachytherapy for clinically localized prostate cancer: results at 7- and 8-year follow-up. *Semin Surg Oncol* 1997; **13**: 438–443.
41 Terk MD, Stock RG, Stone NN. Identification of patients at increased risk for prolonged urinary retention following radioactive seed implantation of the prostate. *J Urol* 1998; **160**: 1379–1382.
42 Beyer DC, Priestley Jr JB. Biochemical disease-free survival following 125I prostate implantation. *Int J Radiat Oncol Biol Phys* 1997; **37**: 559–563.
43 Merrick GS *et al*. Prophylactic versus therapeutic alpha-blockers after permanent prostate brachytherapy. *Urology* 2002; **60**: 650–655.
44 Merrick GS *et al*. Temporal resolution of urinary morbidity following prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2000; **47**: 121–128.
45 Hu K, Wallner K. Urinary incontinence in patients who have a TURP/TUIP following prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 1998; **40**: 783–786.
46 Merrick GS *et al*. Rectal function following prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2000; **48**: 667–674.
47 Gelblum DY, Potters L. Rectal complications associated with transperineal interstitial brachytherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2000; **48**: 119–124.
48 Augustin H *et al*. Patient self-reporting questionnaire on urological morbidity and bother after radical retropubic prostatectomy. *Eur Urol* 2002; **42**: 112–117.
49 Bates TS, Wright MP, Gillatt DA. Prevalence and impact of incontinence and impotence following total prostatectomy assessed anonymously by the ICS-male questionnaire. *Eur Urol* 1998; **33**: 165–169.
50 Steineck G *et al*. Quality of life after radical prostatectomy or watchful waiting. *N Engl J Med* 2002; **347**: 790–796.
51 Potters L *et al*. Potency after permanent prostate brachytherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2001; **50**: 1235–1242.
52 Merrick GS *et al*. Efficacy of sildenafil citrate in prostate brachytherapy patients with erectile dysfunction. *Urology* 1999; **53**: 1112–1116.
53 Stock RG, Kao J, Stone NN. Penile erectile function after permanent radioactive seed implantation for treatment of prostate cancer. *J Urol* 2001; **165**: 436–439.
54 Jani AB, Hellman S. Early prostate cancer: clinical decision-making. *Lancet* 2003; **361**: 1045–1053.
55 Davis JW *et al*. Quality of life after treatment for localized prostate cancer: differences based on treatment modality. *J Urol* 2001; **166**: 947–952.
56 Fulmer BR *et al*. Prospective assessment of voiding and sexual function after treatment for localized prostate carcinoma: comparison of radical prostatectomy to hormonobrachytherapy with and without external beam radiotherapy. *Cancer* 2001; **91**: 2046–2055.
57 Ash D *et al*. ESTRO/EAU/EORTC recommendations on permanent seed implantation for localized prostate cancer. *Radiother Oncol* 2000; **57**: 315–321.
58 Nag S. Brachytherapy for prostate cancer: summary of American Brachytherapy Society recommendations. *Semin Urol Oncol* 2000; **18**: 133–136.
59 Kestin LL *et al*. Percentage of positive biopsy cores as predictor of clinical outcome in prostate cancer treated with radiotherapy. *J Urol* 2002; **168**: 1994–1999.
60 Crook J *et al*. Factors influencing risk of acute urinary retention after TRUS-guided permanent prostate seed implantation. *Int J Radiat Oncol Biol Phys* 2002; **52**: 453–460.
61 Peschel R, Colberg J. Surgery, brachytherapy and external-beam radiotherapy for early prostate cancer. *Lancet Oncol* 2003; **4**: 233–241.