

Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group

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SUPPLEMENTS

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A large number of studies have been conducted on the primary therapy of prostate cancer but very few randomized controlled trials have been conducted. The comparison of outcomes from individual studies involving surgery (radical prostatectomy or robotic radical prostatectomy), external beam radiation (EBRT) (conformal, intensity modulated radiotherapy, protons), brachytherapy, cryotherapy or high intensity focused ultrasound remains problematic due to the non-uniformity of reporting results and the use of varied disease outcome endpoints. Technical advances in these treatments have also made long-term comparisons difficult. The Prostate Cancer Results Study Group was formed to evaluate the comparative effectiveness of prostate

What's known on the subject? and What does the study add?

Very few comparative studies to date evaluate the results of treatment options for prostate cancer using the most sensitive measurement tools. PSA has been identified as the most sensitive tool for measuring treatment effectiveness. To date, comprehensive unbiased reviews of all the current literature are limited for prostate cancer.

This is the first large scale comprehensive review of the literature comparing risk stratified patients by treatment option and with long-term follow-up. The results of the studies are weighted, respecting the impact of larger studies on overall results. The study identified a lack of uniformity in reporting results amongst institutions and centres.

cancer treatments. This international group conducted a comprehensive literature review to identify all studies involving treatment of localized prostate cancer published during 2000–2010. Over 18 000

papers were identified and a further selection was made based on the following key criteria: minimum/median follow-up of 5 years; stratification into low-, intermediate- and high-risk groups; clinical

and pathological staging; accepted standard definitions for prostate-specific antigen failure; minimum patient number of 100 in each risk group (50 for high-risk group). A statistical analysis (standard deviational ellipse) of the study outcomes suggested that, in terms of biochemical-free progression, brachytherapy provides superior outcome in patients with low-risk disease. For intermediate-risk disease,

the combination of EBRT and brachytherapy appears equivalent to brachytherapy alone. For high-risk patients, combination therapies involving EBRT and brachytherapy plus or minus androgen deprivation therapy appear superior to more localized treatments such as seed implant alone, surgery alone or EBRT. It is anticipated that the study will assist physicians and patients in selecting

treatment for men with newly diagnosed prostate cancer.

KEYWORDS

prostate cancer, brachytherapy, radical prostatectomy, radiotherapy, cryotherapy, protons, biochemical-free progression

INTRODUCTION

The evaluation of treatment options for low-, intermediate- and high-risk prostate cancer has remained difficult primarily because of the lack of randomized trials. In the absence of such studies, patients and physicians have used individual institution treatment results to evaluate the effectiveness of modern treatments. Despite a relatively large number of these retrospective studies, the comparison of surgery (radical prostatectomy [RP] or robotic RP), external beam radiation (EBRT) (conformal, intensity modulated radiotherapy, protons), brachytherapy (low dose rate and high dose rate), cryotherapy or high intensity focused ultrasound is complicated by the non-uniformity of reporting results and the use of varied disease outcome endpoints. Technical advances in these treatments have also made long-term comparisons difficult. The Prostate Cancer Results Study Group (PCRS) was formed to evaluate the comparative effectiveness of prostate cancer treatments using current modern literature results as a basis. The ongoing task of the group is to find comparable studies and present these studies and outcomes in an easily understandable form to interested groups. This initiative is designed to provide physicians, their patients and healthcare providers such as Medicare with comprehensive, evidence-based prostate cancer treatment comparisons in an understandable form. Importantly, uniform *pretreatment* staging criteria are used (rather than the postoperative stage) as this is the information that the patients and clinicians rely on when choosing between the different options. The following is a report of the PCRS findings.

TABLE 1 Keywords used in the literature searches

Category	Search words
General	prostate cancer, prostate cancer treatment(s), prostate cancer therapy(ies)
Brachytherapy	prostate cancer brachytherapy, brachytherapy prostate cancer, prostate brachytherapy, brachytherapy prostate cancer outcomes, prostate cancer brachytherapy outcomes, HDR brachytherapy, high-dose-rate brachytherapy, prostate brachytherapy biochemical failure, prostate brachytherapy biochemical free survival, prostate cancer, prostate cancer treatment outcomes
Surgery	prostate cancer surgery, prostate cancer surgery outcomes, prostate cancer prostatectomy, prostate cancer radical prostatectomy, prostate cancer radical retropubic prostatectomy, prostatectomy, prostatectomy biochemical failure, prostatectomy biochemical free survival, prostate cancer prostatectomy outcomes
HIFU	prostate cancer HIFU, prostate cancer HIFU outcomes, HIFU prostate cancer treatment outcomes, high intensity focused ultrasound, high intensity focused ultrasound prostate cancer, high intensity focused ultrasound prostate cancer outcomes, HIFU prostate cancer biochemical failure, HIFU prostate cancer biochemical free survival
Proton	proton therapy prostate cancer, prostate cancer proton therapy, prostate cancer proton, prostate cancer proton therapy outcomes, prostate cancer proton therapy biochemical free survival, proton therapy prostate, prostate cancer proton therapy biochemical free survival
EBRT	EBRT, EBRT prostate cancer, EBRT prostate cancer outcomes, EBRT prostate cancer biochemical failure, EBRT prostate cancer biochemical free survival, radiation therapy prostate cancer, prostate cancer radiation therapy, prostate cancer radiation therapy outcomes, prostate cancer radiation therapy biochemical failure, prostate cancer radiation therapy biochemical free survival IMRT prostate cancer, IMRT prostate cancer outcomes, IMRT prostate cancer biochemical failure, IMRT prostate cancer biochemical failure, intensity modulated radiation therapy prostate cancer, intensity modulated radiation therapy prostate cancer outcomes, intensity modulated radiation therapy prostate cancer biochemical failure, intensity modulated radiation therapy prostate cancer biochemical free survival
Cryotherapy	cryotherapy, prostate cancer, prostate cryo therapy, prostate cancer cryo therapy

HDR, high dose radiation; HIFU, high intensity focused ultrasound; IMRT, intensity modulated radiation therapy.

PATIENTS AND METHODS

A literature search of prostate cancer papers published during 2000–2010 was conducted to find studies related to treatment of localized prostate cancer. The following four databases were searched: PubMed, Medline, Google Scholar and Elsevier. The keywords used in the searches are shown in Table 1. The search resulted in the identification of over 18 000 prostate cancer related abstracts and papers, which were then screened by the PCRSG for evidence of treatment outcomes. Each paper accepted for inclusion in this comparison study was required to meet a set of minimum criteria established by the PCRSG (Table 2). These criteria were unanimously agreed upon by the expert panel to allow for adequate comparison purposes. The number of patients, the reported period of follow-up, the categorization of patients according to the D'Amico *et al.* [1], Zelefsky *et al.* [2] or the National Comprehensive Cancer Network [3] risk group categories of low, intermediate and high risk were determined from the selected publication. Extracted from each paper were the prostate-specific antigen (PSA) results at reported follow-up. Patients reported as relapse free or reaching surgical definitions of free of disease were considered progression free. Results were then categorized into low-, intermediate- or high-risk groups. Data were plotted by treatment modality or regimen according to the reported duration of follow-up and plotted as PSA progression-free survival.

Statistical analysis of the data involved calculating the standard deviational ellipse (SDE) for each treatment group using R (Package *aspace*, version 3.0, 2011; <http://cran.r-project.org/web/packages/aspace/index.html>). The SDE was centred on the weighted mean for all the data points in the treatment group. The ellipse generated represents 1 SD about the weighted mean where data points were weighted by the natural logarithm of the number of patients in the study. A minimum of four data points was required in order to calculate an SDE.

RESULTS

A total of 848 of the batch of over 18 000 published abstracts were initially identified as treatment-related papers. The percentage

TABLE 2 Criteria for inclusion of a study on treatment of localized prostate cancer

- Patients must be stratified into recognizable pretreatment risk groups, low, intermediate and high risk, using D'Amico, Zelefsky or NCCN stratification
- Standard endpoint used to measure biochemical relapse-free survival: ASTRO, Phoenix and PSA < 0.2 ng/mL (for surgery)
- Clinical staging conducted and not pathological staging alone
- EBRT must be minimum 72 Gy IMRT/conformal
- All treatment modalities considered: brachytherapy (including HDR), surgery, IMRT, HIFU, cryotherapy, protons
- Results published in peer-reviewed journals only
- Low risk accepted minimum number of patients was 100
- Intermediate risk accepted minimum number of patients was 100
- High risk accepted minimum number of patients was 50
- Minimum median follow-up was 5 years

NCCN, National Comprehensive Cancer Network; ASTRO, American Society for Radiation Oncology; IMRT, intensity modulated radiotherapy; HDR, high dose rate; HIFU, high intensity focused ultrasound.

TABLE 3 Number of patients in each treatment group and according to risk group category

Treatment type	No. of patients (no. of studies)		
	Low risk	Intermediate	High
RP	6447 (6)	3696 (4)	5149 (11)
Robotic RP	706 (1)	479 (1)	200 (1)
Seeds alone	8133 (17)	5808 (15)	295 (1)
Seeds + EBRT	726 (1)	1554 (6)	2864 (15)
EBRT + seeds + ADT	–	–	1231 (6)
HDR (seeds)	226 (2)	607 (4)	869 (5)
Protons	388 (2)	162 (1)	–
EBRT alone	4735 (9)	2969 (10)	3828 (11)
HIFU	227 (1)	–	–
Cryotherapy	–	175 (1)	357 (2)
Seeds + ADT	–	165 (1)	–

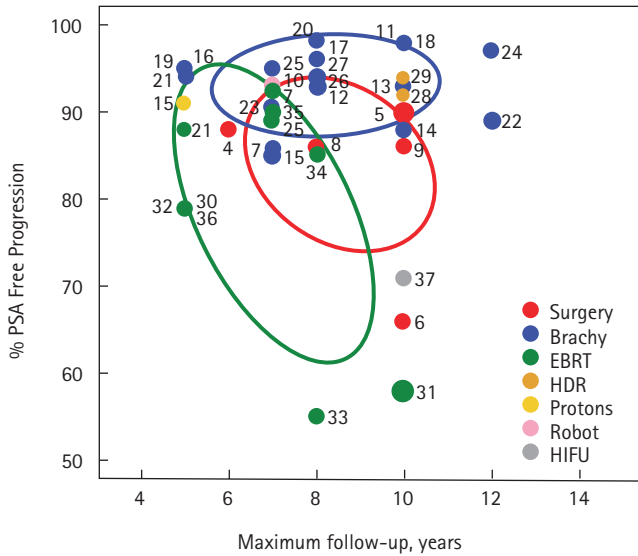
ADT, androgen deprivation therapy; HDR, high dose radiotherapy; HIFU, high intensity focused ultrasound; RP, radical prostatectomy; EBRT, external beam radiation.

of papers by treatment modality meeting PCRSG criteria was as follows: high intensity focused ultrasound 1/30 (3%); robotic radical prostatectomy 3/59 (5%); radical prostatectomy 24/260 (9%); proton therapy 2/13 (15%); cryotherapy 5/31 (16%); EBRT 39/222 (18%); and brachytherapy 66/213 (31%). The total number of patients for each treatment type is shown in Table 3. In total, the studies analysed reported on 52 087 patients.

Outcome from the first analysis is shown in Figs 1–3 and represents the PSA progression-free survival outcomes by

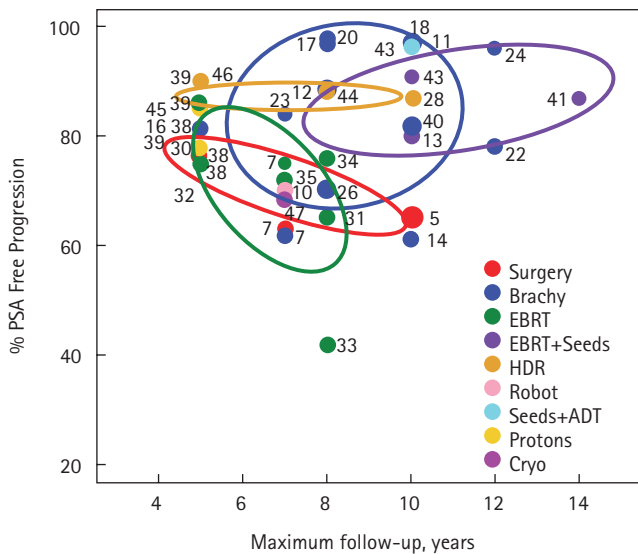
treatment modality for low-, intermediate- and high-risk groups [4–69]. In low-risk patients, higher average PSA progression-free survival was reported for brachytherapy than for RP or EBRT. There was limited reporting with the other therapies although some of the individual studies showed comparable outcomes to RP and EBRT. In intermediate-risk patients, higher average progression-free survival was reported for brachytherapy (permanent seeds and high dose rate) approaches than for RP or EBRT. For high-risk patients combination regimens of androgen deprivation therapy, EBRT and brachytherapy had higher progression-free

FIG. 1. Percentage prostate-specific antigen (PSA)-free progression at maximum follow-up for patients with low-risk prostate cancer treated with a range of therapeutic options. The SDE represents 1 sd about the weighted mean where data points were weighted by the natural logarithm of the number of patients in the study. A minimum of four data points was required in order to calculate an SDE. Brachy, brachytherapy; HDR, high dose radiotherapy; HIFU, high intensity focused ultrasound.



Procedure	No. of patients	Procedure	No. of patients	Procedure	No. of patients
Surgery [4]	336	Brachy [17]	173	Protons [15]	124
Surgery [5]	3283	Brachy [18]	329	Protons [30]	230
Surgery [6]	346	Brachy [19]	586	EBRT [15]	134
Surgery [7]	765	Brachy [20]	173	EBRT [31]	2765
Surgery [8]	1381	Brachy [21]	108	EBRT [32]	421
Surgery [9]	336	Brachy [22]	1345	EBRT [7]	173
Robot [10]	706	Brachy [23]	260	EBRT [21]	108
Brachy [11]	475	Brachy [24]	319	EBRT [33]	485
Brachy [12]	768	Brachy [25]	448	EBRT [25]	281
Brachy [13]	726	Brachy [26]	1444	EBRT [34]	203
Brachy [14]	232	Brachy [27]	319	EBRT [35]	446
Brachy [15]	158	HDR [28]	110	EBRT [36]	227
Brachy [7]	723	HDR [29]	116	HIFU [37]	227
Brachy [16]	273				

FIG. 2. Percentage prostate-specific antigen (PSA)-free progression at maximum follow-up for patients with intermediate-risk prostate cancer treated with a range of therapeutic options. The SDE represents 1 sd about the weighted mean where data points were weighted by the natural logarithm of the number of patients in the study. A minimum of four data points was required in order to calculate an SDE. Brachy, brachytherapy; HDR, high dose radiotherapy; ADT, androgen deprivation therapy; Cryo, cryotherapy; HIFU, high intensity focused ultrasound.



Procedure	No. of patients	Procedure	No. of patients	Procedure	No. of patients
Surgery [5]	2795	Brachy [22]	554	HDR [46]	109
Surgery [38]	336	Brachy [23]	141	Protons [30]	162
Surgery [7]	211	Brachy [24]	144	EBRT [38]	321
Surgery [39]	354	Brachy [39]	256	EBRT [31]	349
Robot [10]	479	Brachy [26]	960	EBRT [32]	137
Brachy [11]	176	EBRT + seeds [11]	460	EBRT [7]	99
Brachy [12]	535	EBRT + seeds [13]	447	EBRT [33]	218
Brachy [14]	369	EBRT + seeds [41]	119	EBRT [33]	218
Brachy [38]	204	EBRT + seeds [42]	157	EBRT [33]	218
Brachy [7]	199	EBRT + seeds [43]	266	EBRT [39]	305
Brachy [16]	123	EBRT + seeds [7]	105	EBRT [34]	255
Brachy [17]	212	Seeds + ADT [43]	165	EBRT [35]	849
Brachy [18]	425	HDR [28]	188	Cryotherapy [47]	175
Brachy [20]	212	HDR [44]	188		
Brachy [40]	1298	HDR [45]	122		

survival than surgery, EBRT or brachytherapy alone.

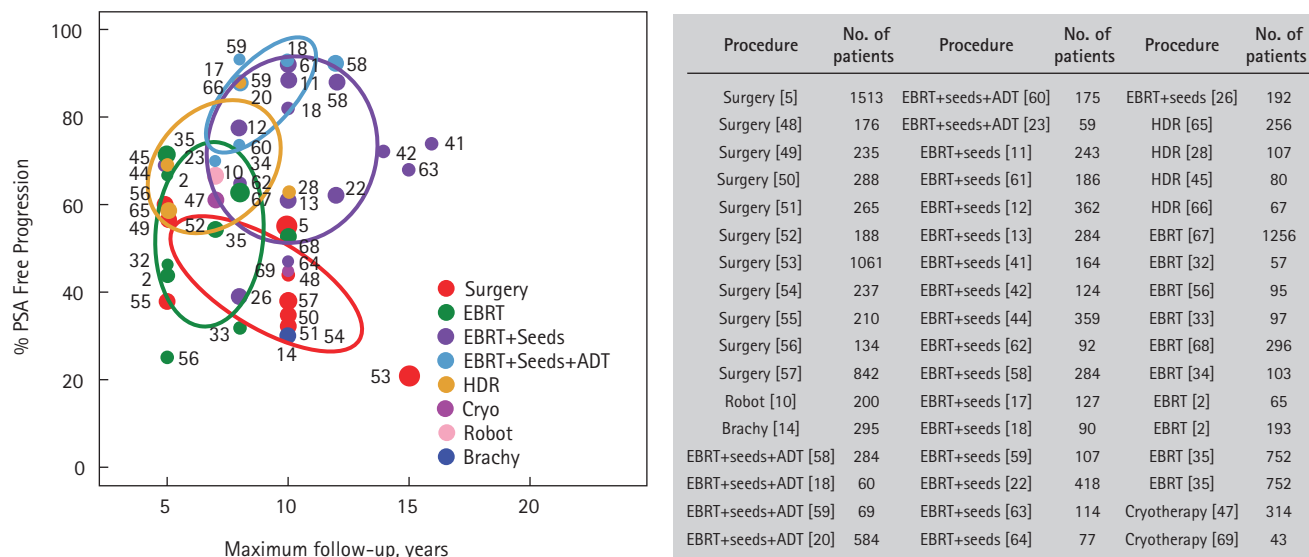
DISCUSSION

Large-scale randomized studies are not yet and are unlikely to be conducted for

prostate cancer. To complicate comparisons, most retrospective studies fail to provide pretreatment risk group stratification, which limits treatment comparisons. Only 17% of the reported papers in this review met the minimal inclusion criteria to allow for comparison. Many surgical studies

stratified patients post-treatment and therefore true comparisons by pretreatment status could not be made. In addition, minimal cancer control endpoints have not been standardized or enforced by journal editors, further creating difficult comparison outcomes across treatment modalities.

FIG. 3. Percentage prostate-specific antigen (PSA)-free progression at maximum follow-up for patients with high-risk prostate cancer treated with a range of therapeutic options. The SDE represents 1 SD about the weighted mean where data points were weighted by the natural logarithm of the number of patients in the study. A minimum of four data points was required in order to calculate an SDE. Brachy, brachytherapy; HDR, high dose radiotherapy; ADT, androgen deprivation therapy; Cryo, cryotherapy; HIFU, high intensity focused ultrasound.



This study evaluated published data from 2000 to 2011 that met the PCRS minimum reporting criteria. All current primary treatment options for each risk group of prostate cancer were included and involved over 52 000 patients. To date only one randomized study has been conducted comparing primary treatment outcomes for brachytherapy and surgery [70], but this study failed to meet the PCRS criteria for inclusion. The current report is the first comprehensive comparative analysis of its kind that looks at all modern treatment outcomes based on the different risk group stratifications, also weighted according to patient numbers. Of note was the observation that risk group definition was uniformly consistent only in the low-risk group. Intermediate- and high-risk group definitions demonstrated some variability. However, studies evaluating the outcomes in high-risk patients based on different definitions have not demonstrated significant differences in outcome after RP [71].

The findings of the study suggest that in terms of biochemical (PSA) free progression, brachytherapy approaches provide superior outcome in patients with low-risk disease. For intermediate-risk disease, the combination of EBRT and brachytherapy

appear equivalent to brachytherapy alone and appear superior to EBRT or surgery; however, selection issues may play a large role in outcomes between these treatment options. For high-risk patients, combination therapies involving EBRT and brachytherapy plus or minus androgen deprivation therapy appear superior to more localized treatments such as seed implant alone, surgery alone or EBRT. No study was found that purely looked at the results of high-risk patients treated with planned surgery and EBRT, so extrapolation on this form of treatment could not be commented upon.

Since it is unlikely that large randomized studies will be conducted, physicians and patients will rely largely upon the use of retrospective studies to compare treatment results. Such reviews will require that studies report on similar patient populations, as determined by pretreatment measurements, and outcomes measured primarily in terms of treatment effect (e.g. PSA). Since only a small percentage of studies in this work met minimum comparable reporting standards, the PCRS encourages editors and reviewers to advocate that future authors be required to report results based on standardized pretreatment risk classification and PSA-based outcome measures. One of the

limitations of the current study is that, despite attempts to compare data by using pre-selected rigorous inclusion and exclusion criteria, we found that some of the included studies may not be directly comparable based on other factors.

This study should provide cancer control information to physicians and patients attempting to make an ultimate treatment decision. It is acknowledged that other factors can also significantly affect a patient's and physician's decision on the type of prostate cancer treatment. This report is based on accepted standard surgical and radiation definitions of PSA failures. It is also acknowledged that differences between definitions of PSA outcomes between various treatment modalities make the final conclusion less certain. As part of an ongoing process, the literature review will be updated bi-yearly by the PCRS and further information is provided on the website: <http://www.prostatecancertreatmentcenter.com/>.

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CONFLICT OF INTEREST

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REFERENCES

- 1 **D'Amico AV, Whittington R, Malkowicz SB et al.** Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998; **280**: 969–74
- 2 **Zelevsky MJ, Fuks Z, Hunt M et al.** High dose radiation delivered by intensity modulated conformal radiotherapy improves the outcome of localized prostate cancer. *Urology* 2001; **166**: 876–81
- 3 **National Comprehensive Cancer Network.** Prostate Cancer treatment guidelines for patients, 2007. <http://www.psa-rising.com/download/nccnguidelines.pdf>
- 4 **Bhatta D, Reuther AM, Zippe C, Klein EA.** No difference in 6 year biochemical failure rates with or without pelvic lymph nodes during radical prostatectomy in low-risk patients with prostate cancer. *Urology* 2004; **63**: 528–31
- 5 **Boorjian S, Karnes RJ, Rangel LJ, Bergstralh EJ, Blute ML.** Mayo Clinic validation of the d'Amico risk group classification for predicting survival following radical prostatectomy. *J Urol* 2008; **179**: 1354–61
- 6 **Kane CJ, Im R, Amling CL et al.** Outcomes after radical prostatectomy among men who are candidates for active surveillance: results from the SEARCH database. *Urology* 2010; **76**: 695–700
- 7 **Kupelian P, Kuban D, Thames H 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* 2004; **58**: 25–33
- 8 **Nguyen PL, Chen MH, Catalona WJ et al.** Biochemical recurrence after radical prostatectomy for prevalent versus incident cases of prostate cancer: implications for management. *Cancer* 2008; **113**: 3146–52
- 9 **Weight C, Reuther A, Gunn P et al.** Limited pelvic lymph node dissection does not improve biochemical relapse free survival at 10 years after radical prostatectomy in patients with low risk prostate cancer. *J Urol* 2008; **71**: 141–5
- 10 **Menon M, Bhandari M, Gupta N et al.** Biochemical recurrence following robot-assisted radical prostatectomy: analysis of 1384 patients with a median 5-year follow-up. *Eur Urol* 2010; **58**: 838–46
- 11 **Bittner N, Merrick GS, Galbreath RW et al.** Primary causes of death after permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2008; **72**: 433–40
- 12 **Burri RJ, Ho AY, Forsythe K, Cesaretti JA, Stone NN, Stock RG.** Young men have equivalent biochemical outcomes compared with older men after treatment with brachytherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2010; **77**: 1315–21
- 13 **Critz FA, Levinson K.** 10-year disease free survival rates after simultaneous irradiation for prostate cancer with a focus on calculation and methodology. *J Urol* 2004; **172**: 2232–8
- 14 **Hinnen KA, Battermann JJ, van Roermund JG et al.** Long-term biochemical and survival outcome of 921 patients treated with 1125 permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2010; **76**: 1433–8
- 15 **Jabbari S, Weinberg VK, Shinohara K et al.** Equivalent biochemical control and improved prostate-specific antigen nadir after permanent seed brachytherapy versus high-dose three-dimensional conformal radiotherapy and high-dose conformal proton beam radiotherapy boost. *Int J Radiat Oncol Biol Phys* 2010; **76**: 36–42
- 16 **Martin AG, Roy J, Beaulieu L et al.** Permanent prostate implant using high activity seeds and inverse planning with fast simulated annealing algorithm: a 12-year Canadian experience. *Int J Radiat Oncol Biol Phys* 2007; **67**: 334–41
- 17 **Merrick GS, Butler WM, Wallner KE et al.** Prognostic significance of perineural invasion on biochemical progression-free survival after prostate brachytherapy. *Urology* 2005; **66**: 1048–53
- 18 **Merrick GS, Butler WM, Wallner KE, Galbreath RW, Allen ZA, Adamovich E.** Androgen deprivation therapy does not impact cause-specific overall survival after permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2006; **65**: 669–77
- 19 **Morris WJ, Keyes M, Palma D et al.** Population-based study of biochemical and survival outcomes after permanent 125I brachytherapy for low- and intermediate-risk prostate cancer. *Urology* 2009; **73**: 860–5
- 20 **Moyad MA, Merrick GS, Butler WM et al.** Statins especially atorvastatin, may favorably influence clinical presentation and biochemical progression-free survival after brachytherapy for clinically localized prostate cancer. *Urology* 2005; **66**: 1150–4
- 21 **Pickles T, Keyes M, Morris WJ.** Brachytherapy or conformal external radiotherapy for prostate cancer: a single-institution matched-pair analysis. *Int J Radiat Oncol Biol Phys* 2010; **76**: 43–9
- 22 **Potters L, Morgenstern C, Calugaru E et al.** 12-year outcomes following permanent prostate brachytherapy in patients with clinically localized prostate cancer. *J Urol* 2005; **173**: 1562–6
- 23 **Stone NN, Stock RG, Cesaretti JA, Unger P.** Local control following permanent prostate brachytherapy: effect of high bed on biopsy results and oncologic outcomes. *Int J Radiat Oncol Biol Phys* 2010; **76**: 355–60
- 24 **Taira AV, Merrick GS, Galbreath RW, Wallner KE, Butler WM.** Natural history of clinically staged low and intermediate risk prostate cancer treated with monotherapy permanent interstitial brachytherapy. *Int J Radiat Oncol Biol Phys* 2010; **76**: 349–54
- 25 **Zelevsky MJ, Yamada Y, Pei X et al.** Comparison of tumor control and toxicity outcomes of high-dose intensity-modulated radiotherapy and brachytherapy for patients with favorable risk prostate cancer. *Urology* 2011; **77**: 986–90
- 26 **Zelevsky M, Kuban D, Levy L et al.** Multi-institutional analysis of long-term outcome for stages T1–T2 prostate cancer treated with permanent seed implantation. *Int J Radiat Oncol Biol Phys* 2007; **67**: 327–33
- 27 **Zelevsky M, Yamada Y, Cohen, G et al.** Five-year outcome of intraoperative

- conformal permanent I-125 interstitial implantation for patients with clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2007; **67**: 65–70
- 28 Demanes DJ, Brandt D, Schour L, Hill DR. Excellent results from high dose rate brachytherapy and external beam prostate cancer are not improved by androgen deprivation. *Am J Clin Oncol* 2009; **32**: 342–47
- 29 Ellis R, Kaminsky DA, Zhou EH *et al*. Ten-year outcomes: the clinical utility of single photon emission computed tomography/computed tomography capromab pendetide (Prostascint) in a cohort diagnosed with localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2011; **81**: 29–34
- 30 Rossi CJ. Conformal proton beam radiation therapy for prostate cancer: concepts and clinical results. *Community Oncology* 2007; **4**: 235–45
- 31 Kuban DA, Thames HD, Levy LB *et al*. Long-term multi-institutional analysis of stage T1–T2 prostate cancer treated with radiotherapy in the PSA era. *Int J Radiat Oncol Biol Phys* 2003; **57**: 915–28
- 32 Kupelian P, Kuban D, Thames H *et al*. Improved biochemical relapse-free survival with increased radiation doses in patients with localized prostate cancer: the combined experience of nine institutions in 1994 and 1995. *Int J Radiat Oncol Biol Phys* 2005; **61**: 415–9
- 33 Thames H, Kuban D, DeSilvio M *et al*. Increasing external beam dose for T1–T2 prostate cancer: effect on risk groups. *Int J Radiat Oncol Biol Phys* 2006; **65**: 975–81
- 34 Zelefsky M, Chan H, Hunt M *et al*. Long-term outcome of high dose intensity modulated radiation therapy for patients with clinically localized prostate cancer. *J Urol* 2006; **176**: 1415–9
- 35 Zelefsky M, Yamada Y, Fuks Z *et al*. Long-term results of conformal radiotherapy for prostate cancer: impact of dose escalation in biochemical tumor control and distant metastases-free survival outcomes. *Int J Radiat Oncol Biol Phys* 2008; **71**: 1028–33
- 36 Zietman AL, DeSilvio ML, Slater JD *et al*. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA* 2005; **294**: 1233–9
- 37 Zietman MJ, Yamada Y, Pei X *et al*. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from Proton Radiation Oncology Group/American College of Radiology 95–09. *J Clin Oncol* 2010; **28**: 1106–11
- 38 Klein EA, Ciezki J, Kupelian PA, Mahadevan A. Outcomes for intermediate risk prostate cancer: are there advantages for surgery, external beam, or brachytherapy. *Urol Oncol* 2009; **27**: 67–71
- 39 Vassil AD, Murphy ES, Reddy CA *et al*. Five year biochemical recurrence free survival for intermediate risk prostate cancer after radical prostatectomy, external beam radiation therapy or permanent seed implantation. *Urology* 2010; **76**: 1251–7
- 40 Munro NP, Al-Qaisieh B, Bownes P *et al*. Outcomes for Gleason 7, intermediate risk, localized prostate cancer treated with iodine-125 monotherapy over 10 years. *Radiother Oncol* 2010; **96**: 34–7
- 41 Dattoli M, Wallner K, True L, Cash J, Sorace R. Long-term outcomes after treatment with brachytherapy and supplemental conformal radiation for prostate cancer patients having intermediate and high-risk features. *Cancer* 2007; **110**: 551–5
- 42 Dattoli M, Wallner K, True L, Bostwick D, Cash J, Sorace R. Long term outcomes for patients with prostate cancer having intermediate and high risk disease, treated with combination external radiation and brachytherapy. *J Oncol* 2010; **2010**: 471375
- 43 Ho AY, Burri RJ, Cesaretti JA, Stone NN, Stock RG. Radiation dose predicts for biochemical control in intermediate-risk prostate cancer patients with low-dose-rate brachytherapy. *Int J Radiat Oncol Biol Phys* 2009; **75**: 16–22
- 44 Galalae RM, Martinez A, Mate T *et al*. Long-term outcome by risk factors using conformal high dose brachytherapy (HDR-BT) boost with or without neoadjuvant androgen suppression for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2004; **58**: 1048–55
- 45 Galalae RM, Martinez A, Nuernberg N *et al*. Hypofractionated conformal HDR brachytherapy in hormone naive men with localized prostate cancer. Is escalation to very high biologically equivalent dose beneficial in all prognostic risk groups? *Strahlenther Onkol* 2006; **181**: 135–41
- 46 Phan TP, Syed AM, Puthawala A, Sharma A, Khan F. High dose rate brachytherapy as a boost for the treatment of localized prostate cancer. *J Urol* 2002; **177**: 123–7
- 47 Bahn DK, Lee F, Badalament R, Kumar A, Greski J, Chernick M. Targeted cryoablation of the prostate: 7-year outcomes in the primary treatment of prostate cancer. *Urology* 2002; **60**: 3–11
- 48 Carver BS, Bianco FJ Jr, Scardino PT, Eastham JA. Long-term outcome following radical prostatectomy in men with clinical stage T3 prostate cancer. *J Urol* 2006; **176**: 564–8
- 49 Hsu CY, Joniau S, Roskams T, Oyen R, Van Poppel H. Comparing results after surgery in patients with clinical unilateral T3a prostate cancer treated with or without neoadjuvant androgen-deprivation therapy. *BJU Int* 2006; **99**: 311–4
- 50 Loeb S, Smith ND, Roehl KA, Catalona WJ. Intermediate-term potency, continence, and survival outcomes of radical prostatectomy for clinically high-risk or locally advanced prostate cancer. *Urology* 2007; **69**: 1170–5
- 51 Magheli A, Rais-Bahrami S, Peck HJ *et al*. Importance of tumor location in patients with high preoperative prostate specific antigen levels (greater than 20 ng/ml) treated with radical prostatectomy. *J Urol* 2007; **178**: 1311–5
- 52 Mian BM, Troncoso P, Okihara K *et al*. Outcome of patients with Gleason score 8 or higher prostate cancer following radical prostatectomy alone. *J Urol* 2002; **167**: 1675–80
- 53 Pierorazio PM, Guzzo TJ, Han M *et al*. Long-term survival after radical prostatectomy for men with high Gleason sum in pathologic specimens. *Urology* 2010; **76**: 715–21
- 54 Roehl KA, Han M, Ramos CG, Antenor JA, Catalona WJ. Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3478 consecutive patients: long-term results. *J Urol* 2004; **172**: 910–4
- 55 Rubio-Briones J, Iborra I, Trassierra M *et al*. Metastatic progression,

- cancer-specific mortality and need for secondary treatments in patients with clinically high-risk prostate cancer treated initially with radical prostatectomy. *Actas Urol Esp* 2010; **34**: 610–7
- 56 **Stokes SH.** Comparison of biochemical disease-free survival of patients with localized carcinoma of the prostate undergoing radical prostatectomy, transperineal ultrasound-guided radioactive seed implantation, or definitive external beam irradiation. *Int J Radiat Oncol Biol Phys* 2000; **471**: 129–36
- 57 **Ward JF, Slezak JM, Blute ML, Bergstralh EJ, Zincke H.** Radical prostatectomy for clinically advanced (cT3) prostate cancer since the advent of prostate-specific antigen testing: 15-year outcome. *BJU Int* 2005; **95**: 751–6
- 58 **Merrick GS, Butler WM, Galbreath RW et al.** Prostate cancer death is unlikely in high-risk patients following quality permanent interstitial brachytherapy. *BJU Int* 2011; **107**: 226–32
- 59 **Merrick GS, Butler WM, Wallner KE et al.** Impact of supplemental external beam radiotherapy and/or androgen deprivation therapy on biochemical outcome after permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2005; **61**: 32–43
- 60 **Stock RG, Cesaretti JA, Hall SJ, Stone NN.** Outcomes for patients with high-grade prostate cancer treated with a combination of brachytherapy, external beam radiotherapy and hormonal therapy. *BJU Int* 2009; **104**: 1631–6
- 61 **Bittner N, Merrick GS, Wallner KE, Butler WM, Galbreath R, Adamovich E.** Whole-pelvis radiotherapy in combination with interstitial brachytherapy: does coverage of the pelvic lymph nodes improve treatment outcome in high-risk prostate cancer? *Int J Radiat Oncol Biol Phys* 2010; **76**: 1078–84
- 62 **Kollmeier MA, Stock RG, Stone N.** Biochemical outcome after prostate brachytherapy with 5-year minimal follow-up: importance of patient selection and implant quality. *Int J Radiat Oncol Biol Phys* 2003; **57**: 645–53
- 63 **Sylvester JE, Grimm PD, Blasko JC et al.** 15-year biochemical relapse free survival in clinical stage T1–T3 prostate cancer following combined external beam radiotherapy and brachytherapy; Seattle experience. *Int J Radiat Oncol Biol Phys* 2007; **67**: 57–64
- 64 **Sylvester JE, Blasko JC, Grimm PD, Meier R, Malmgren JA.** Ten-year biochemical relapse-free survival after external beam radiation and brachytherapy for localized prostate cancer: the Seattle experience. *Int J Radiat Oncol Biol Phys* 2003; **57**: 944–52
- 65 **Deger S, Boehmer D, Türk I et al.** High dose rate brachytherapy of localized prostate cancer. *Eur Urol* 2002; **41**: 420–6
- 66 **Pellizzon AC, Salvajoli JV, Novaes P et al.** The relationship between the biochemical control outcomes and the quality of planning of high-dose rate brachytherapy as a boost to external beam radiotherapy for locally and locally advanced prostate cancer using the RTOG-ASTRO Phoenix definition. *Int J Med Sci* 2008; **5**: 113–20
- 67 **Kuban DA, Tucker SL, Dong L et al.** Long term results of the MD Anderson randomized dose escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys* 2008; **70**: 67–74
- 68 **Zeleftsky MJ, Yamada Y, Kollmeier MA, Shippy AM, Nedelka MA.** Long term outcome following three-dimensional conformal intensity modulated external-beam radiotherapy for clinical stage T3 prostate cancer. *Eur Urol* 2008; **53**: 1172–9
- 69 **Cohen JK, Miller RJ Jr, Ahmed S, Lotz MJ, Baust J.** Ten-year biochemical disease control for patients with prostate cancer treated with cryosurgery as primary therapy. *Urology* 2008; **71**: 515–8
- 70 **Giberti C, Chiono L, Gallo F, Schenone M, Gastaldi E.** Radical retropubic prostatectomy versus brachytherapy for low-risk prostatic cancer: a prospective study. *World J Urol* 2009; **27**: 607–612
- 71 **Nguyen CT, Reuther AM, Stephenson AJ, Klein EA, Jones JS.** The specific definition of high risk prostate cancer has minimal impact on biochemical relapse-free survival. *J Urol* 2009; **181**: 75–80

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Abbreviations: RP, radical prostatectomy; EBRT, external beam radiation; PCRS, Prostate Cancer Results Study Group; SDE, standard deviation ellipse.