BJUI SUPPLEMENTS

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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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 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

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.

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 (PCRSG) 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 PCRSG 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.

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

	No. of patients (no. of studies)		
Treatment type	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)	–

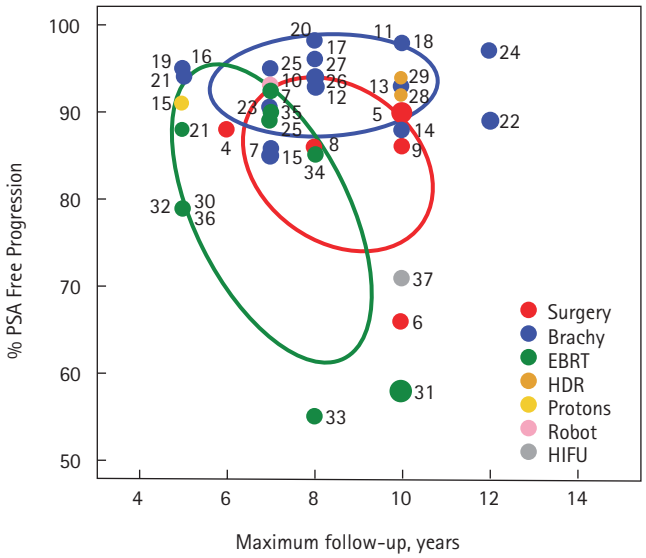
ADT, androgen deprivation therapy; HDR, high dose radiotherapy; HIFU, high intensity focused ultrasound; RP, radical prostatectomy; EBRT, external beam radiation.

RESULTS

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

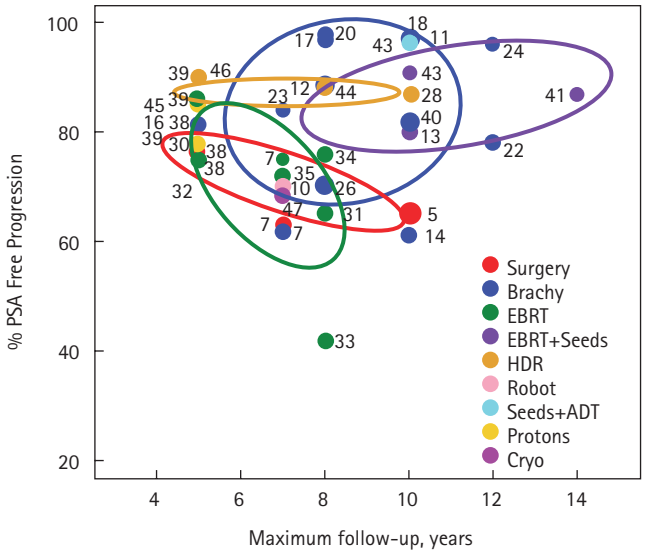
Outcome from the first analysis is shown in Figs 1–3 and represents the PSA progression-free survival outcomes by treatment modality for low-, intermediate- and high-risk groups [4–69]. In low-risk patients, higher average PSA progression-free survival was reported for brachytherapy than for RP or EBRT. 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.



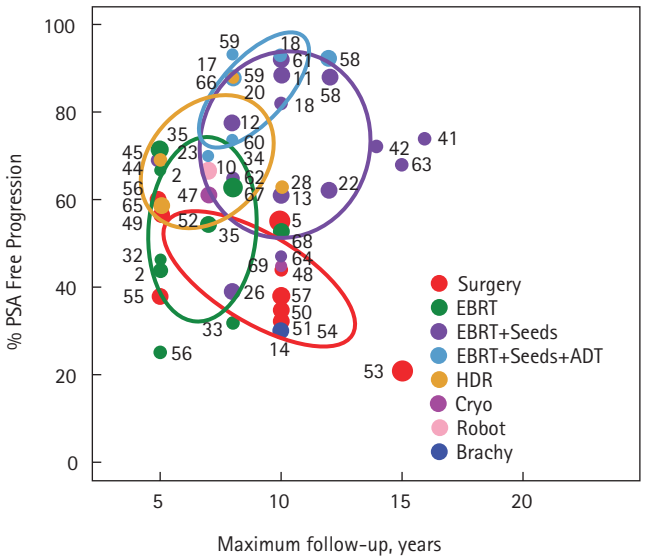
Procedure	No. of patients	Procedure	No. of patients	Procedure	No. of patients
Surgery [5]	2795	Brachy [22]	554	HDR [46]	109
Surgery [38]	336	Brachy [23]	141	Protons [30]	162
Surgery [7]	211	Brachy [24]	144	EBRT [38]	321
Surgery [39]	354	Brachy [39]	256	EBRT [31]	349
Robot [10]	479	Brachy [26]	960	EBRT [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.



Procedure	No. of patients	Procedure	No. of patients	Procedure	No. of patients
Surgery [5]	1513	EBRT+seeds+ADT [60]	175	EBRT+seeds [26]	192
Surgery [48]	176	EBRT+seeds+ADT [23]	59	HDR [65]	256
Surgery [49]	235	EBRT+seeds [11]	243	HDR [28]	107
Surgery [50]	288	EBRT+seeds [61]	186	HDR [45]	80
Surgery [51]	265	EBRT+seeds [12]	362	HDR [66]	67
Surgery [52]	188	EBRT+seeds [13]	284	EBRT [67]	1256
Surgery [53]	1061	EBRT+seeds [41]	164	EBRT [32]	57
Surgery [54]	237	EBRT+seeds [42]	124	EBRT [56]	95
Surgery [55]	210	EBRT+seeds [44]	359	EBRT [33]	97
Surgery [56]	134	EBRT+seeds [62]	92	EBRT [68]	296
Surgery [57]	842	EBRT+seeds [58]	284	EBRT [34]	103
Robot [10]	200	EBRT+seeds [17]	127	EBRT [2]	65
Brachy [14]	295	EBRT+seeds [18]	90	EBRT [2]	193
EBRT+seeds+ADT [58]	284	EBRT+seeds [59]	107	EBRT [35]	752
EBRT+seeds+ADT [18]	60	EBRT+seeds [22]	418	EBRT [35]	752
EBRT+seeds+ADT [59]	69	EBRT+seeds [63]	114	Cryotherapy [47]	314
EBRT+seeds+ADT [20]	584	EBRT+seeds [64]	77	Cryotherapy [69]	43

This study evaluated published data from 2000 to 2011 that met the PCRSG 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 PCRSG 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 PCRSG 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 PCRSG and further information is provided on the website: http://www.prostatecancertreatmentcenter.com/.

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CONFLICT OF INTEREST

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