Curr Urol Rep (2015) 16: 27
DOI 10.1007/s11934-015-0504-z

UROSURGERY (J COLLINS, SECTION EDITOR)

Organ-Confined Prostate Cancer: Are We Moving Towards More or Less Radical Surgical Intervention?

Daniel J. Stevens · Naomi L. Sharma · Ashutosh K. Tewari · Roger Kirby · Prasanna Sooriakumaran

Published online: 17 March 2015

Abstract Treatment possibilities for clinically localised prostate cancer include radical prostatectomy (RP), external beam radiotherapy, brachytherapy, focal therapy and active surveillance. Conflicting and methodologically flawed observational data from the last two decades have led to uncertainty as to the best oncological option. However, recently, there has been a series of high-quality studies that point to disease specific and overall survival advantages for those men undergoing RP. This article reviews the latest evidence and argues that at the current time, RP must be considered the gold standard treatment for the majority of men with clinically localised prostate cancer.

Keywords Radical prostatectomy · Prostate cancer · Radiotherapy · Brachytherapy · Urosurgery

This article is part of the Topical Collection on *Urosurgery*

D. J. Stevens
Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, UK

D. J. Stevens · N. L. Sharma · P. Sooriakumaran (✉)
Department of Urology, Oxford University Hospitals NHS Trust, Oxford, UK
e-mail: prasanna.sooriakumaran@nds.ox.ac.uk

P. Sooriakumaran
Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK

A. K. Tewari
Department of Urology, Mount Sinai School of Medicine, New York, NY, USA

R. Kirby
The Prostate Centre, London, UK

P. Sooriakumaran
Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden

Introduction

Prostate cancer (PCa) remains the most frequently diagnosed cancer in men in developed countries. There were 41,763 new cases diagnosed in the UK in 2011 and 10,793 deaths [1•]. The majority of men with PCa have clinically localised disease, and most of these men currently undergo radical treatment [2]. Despite millions of men having undergone radical prostatectomy (RP), the surgical treatment of PCa remains controversial. There have been two significant randomised trials comparing RP with watchful waiting (WW). The Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) randomised 695 men to RP or WW. It showed a significant survival benefit for those men undergoing RP as compared with observation at 15 years of follow-up with a RR of 0.56 (0.41–0.77) [3••]. By contrast, the Prostate Cancer Intervention versus Observation Trial (PIVOT) showed that RP did not significantly reduce prostate cancer-specific or overall mortality after 12 years [4••]. However, subgroup analyses of young men with intermediate- and high-risk disease undergoing RP did suggest a reduction in overall mortality with a RR of 0.71 (0.54–0.92). There have been no randomised trials that have reported oncological outcomes of RP vs radiotherapy (RT) so far; the ProtecT study has randomised 1643 men to RP vs RT vs active surveillance (AS) in a 1:1:1 ratio but will not report until 2016 [5]. The other recently established study, SPCG-15, which has just started randomising men with T3 disease to RP +/− RT vs RT plus hormone treatment, will not generate final results until 2027. Without current high-quality and consistent evidence from randomised trials, PCa clinicians are left to interpret the large body of observational data when advising their patients.

Many authorities support AS as an alternative to immediate intervention that may help limit the potential harms caused by overtreatment [6]. Some even believe that low-risk patients

should be managed by AS, high-risk patients should undergo RT and hormone treatment, and that hence RP will be limited to men with intermediate-risk disease who choose it instead of RT. In contrast with this viewpoint and taking the current body of evidence as a whole, we would advocate that the majority of men with clinically localised PCa should consider RP as their first-choice treatment. In this review, we aim to discuss the recent evidence to support this; we contend that RP, far from diminishing in indication, will in fact be used in greater numbers on both ends of the clinically localised disease spectrum. Indeed, a recent survey of urologists in Europe revealed RP to be the preferred first step of a multi-modal treatment approach for high-risk localised prostate cancer [7].

In the last two decades, there have been several pieces of research comparing outcomes of RP with other treatment options such as RT (both external beam and brachytherapy) and AS [8•, 9–13]. The results of these studies have often conflicted and been limited by the quality of the initial dataset and the statistical analyses employed. However, in the last year or so, there have been a number of higher quality studies comparing RP with RT and/or watchful waiting that add to this body of evidence. The first of these by Sun et al. published in 2014 used US Surveillance, Epidemiology and End Results (SEER) data to examine and compare cancer-specific mortality (CSM) and 10-year overall survival (OS) in men >65 years of age with clinically localised PCa [14•]. These men were treated with RP, RT or observation, and the results were analysed with regard to life expectancy. Sixty-seven thousand eighty-seven men with localised PCa were treated with RP (23 %), RT (50 %) or observation (27 %). Attempting to control for local area treatment pattern and unmeasured residual confounders, the data demonstrated that in men with <10 years life expectancy, RP and RT had significantly better OS rates than those that underwent observation regardless of tumour stage. There was no significant difference in OS between RP and RT groups, although it is worth noting that of 7706 men with a life expectancy of <10 years, only 3.4 % of men had a RP. In the cohort of men with a life expectancy of >10 years, the OS rates were significantly better among RP-treated patients compared to their RT and observation counterparts, irrespective of tumour stage. CSM rates were lower for RP in both life expectancy cohorts when compared with observation and lower when compared to RT with the exception of men with >10 years life expectancy and a T2a/b PCa. In multivariable Cox regression analyses, RP-treated men were 34 and 41 % less likely to die relative to their RT and observation counterparts, respectively. However, the results of this study have to be interpreted in the context of the populations studied. It is likely that many Medicare beneficiaries were denied RP for medical reasons independent of their PCa diagnosis, and patients' life expectancies was calculated purely on chronological age. Similarly, as stated by the authors, despite advanced statistical methods to adjust for unmeasured confounders, it is unlikely that all biases were accounted for. Indeed, the definition of the observation group was the absence of active treatment codes, and thus the authors were unable to distinguish those men who actually underwent AS. Another limitation of this study was the absence of accurate PSA values or biopsy results meaning risk stratification using these characteristics was not possible.

Hoffman et al. have also recently published observational data based on SEER data [15•]. They analysed a cohort of men from the population-based Prostate Cancer Outcomes Study which included men aged 55 to 74 who underwent either RP or RT within 1 year of diagnosis. Out of 1500 men, there were 568 deaths after 15 years of follow-up, 104 of which were attributed to PCa. RP was associated with statistically significant advantages for overall and PCa-specific mortality. Mortality benefits for RP over RT were found after pair-matching cases based on propensity scores as well as in subgroup analyses based on age, tumour characteristics and comorbidity. However, the study reflects treatment outcomes and modalities being offered in the mid-1990s, and there may also be residual selection bias due to unmeasured confounders. Again, detailed information on the patient's biopsy results make accurate risk stratification difficult, and although the authors used the Charlson index for comorbidity scoring, this is increasingly recognised as a crude measure with some authors suggesting the score needs modification to better predict outcomes in prostate cancer [16]. Notwithstanding these aforementioned limitations, the possibility though remains that these US analyses have uncovered a true survival advantage for RP over RT.

In order to address some of the limitations detailed above and to try and answer this question with the best available evidence, Sooriakumaran et al. recently published a comprehensive analysis of survival outcomes using high-quality observational data and robust statistical techniques [17••]. They abstracted data from the PCBaSe registry comprised of the Swedish National Prostate Cancer Register (NPCR) linked to 8 other national registries. The NPCR has been shown to cover >98 % of all PCa cases diagnosed in Sweden since 1998, with limited coverage in some regions since 1996 [17••]. Linkage to the In-patient Register, the Cause of Death Register and other validated datasets provided the authors with the unique opportunity to access virtually complete clinico-pathologico-demographic data on virtually all PCa cases in Sweden. The authors extracted data on all clinically localised PCa cases within PCBaSe and compared mortality outcomes among patients who received RP vs RT as their primary management. This led to a study cohort of 34,515 men with a median follow-up of 5.37 years. The most striking finding from this was that all adjustments from all of the statistical methods used to adjust for confounding, including comorbidities, suggested RP was associated with lower prostate cancer-specific mortality than RT, especially in younger, fitter

men with intermediate- or high-risk disease. Low-risk men, especially if they were older, had very low probability of dying from PCa, and therefore, survival differences were clinically negligible. Despite being retrospective, this study had the added strength of exposure data being recorded before the outcome and follow-up being carried out blinded to the exposure status. However, its limitations must be acknowledged and include that no information was obtained on the actual treatment received, instead relying on 'planned treatment'. Similarly, no data was available with regard to secondary treatments, and thus, the study can only comment on potentially best first-line therapy. Adjustment by year of surgery suggested though that the advantages of RP over RT were preserved over the course of the study, giving weight to the assertion that potentially lower doses of RT given in the early study years were not the cause for the oncological differences obtained. Finally, all statistical models (traditional multivariable, propensity score adjusted, inverse probability of treatment weights and propensity matching) led to similar results, giving a reasonable level of confidence in the validity of the results employed. Nonetheless, it is entirely possible that at least some of the oncological benefit seen with RP was the result of confounding by indication, especially as the treatment groups at baseline were rather different in casemix. Statistical methodologies can only partially address this [18], and the only way to completely eliminate this is with a RCT, as discussed by Rane in the editorial accompanying the original paper [19].

Another recent seminal publication from 2014, this time from Bill-Axelson et al., presented extended follow-up data from SPCG-4; 695 men were randomised to either arm as described in previous articles [3••]. After up to 23.2 years of follow-up, there was an absolute difference in relative risk of death of 11 % for the men who underwent radical prostatectomy compared to the men who had watchful waiting. The benefit of surgery with respect to death from prostate cancer was largest in men younger than 65 years of age and in those with intermediate-risk prostate cancer, similar to the PCBaSe and prior observational studies comparing surgery with radiotherapy quoted above.

Despite the substantial reduction in mortality in the RP group shown in the updated SPCG-4 study, more than 40 % of the men in the AS group had no disease progression and required no additional treatment despite a median follow-up of 13 years, and thus, it is important to consider factors other than survival when counselling patients with regard to their prostate cancer treatment. Indeed, a recent study examining the quality of life of 1200 post-RP patients in Canada demonstrated that overall health-related quality of life, sexual drive, sexual function, energy and bladder control do not return to preoperative levels within 30 months of RP [20]. Similarly, Sanda et al. published a seminal paper in *NEJM* that highlights the distinct pattern of change in quality of life related to urinary, sexual and bowel function that can be attributed to the different prostate cancer treatments [21]. Although traditionally clinicians may associate complications more closely with surgical procedures, it is important to highlight the significant post-treatment morbidity associated with RT also. Nam et al. examined the patient records of 32,465 men who underwent either RP or RT in Canada and found that RT cases had higher incidence of complications for hospital admissions, rectal or anal procedures, further open surgical procedures and secondary cancers at 5 years compared to men undergoing RP [22]. Further, in recent times, significant advances have been made in the surgical technique of RP, including the introduction of minimally invasive surgery. In 1991, the first laparoscopic prostatectomy was performed [23], and more recently, robotic-assisted radical prostatectomy has been introduced with cases performed in the UK since 2004 [24].

Studies have shown that the benefits of robotic surgery over open RP include reduced overall complication rates, specifically with regard to hospital stay and blood loss, as well as likely improved potency and continence rates [25, 26]. The best functional and oncological outcomes appear to be reported by high-volume referral centres, rather than those derived from national databases, which include many low-volume centres [26]. Due to high installation costs, robotic surgery has followed the trend towards centralisation of cancer services in the UK and robotic centres (n=28) are more likely to be high-volume specialist centres with skilled surgeons, as noted in the BAUS audit of RP in the UK [27]. A recent publication of 5-year biochemical outcomes after robotic prostatectomy showed that surgeon volume was more predictive of outcome than PSA, stressing the importance of the surgeon and not just the tool used [28]. Therefore, improvements in surgical technique and technology, as well as centralisation of services into the hands of fewer and higher volume surgeons and centres, all further the case for RP in men with localised PCa.

We have discussed above that men with low-risk organ-confined PCa are increasingly being offered AS by many practitioners as an alternative to radical treatment. In theory, only men whose disease status is reclassified during AS, or men who cannot live with the diagnosis of untreated cancer, will ultimately be treated [29]. However, the types of monitoring and their optimal frequency in AS regimens are certainly yet to be defined. It is also important to consider whether follow-up should vary on the basis of patient and tumour characteristics [30]. The development of multiparametric magnetic resonance imaging (mpMRI) is a welcome advance, and there is emerging evidence for its role in the surveillance of prostate lesions over time. A recent systematic review published in 2014 examined this and concluded that while MRI has the potential to be a key part of the AS strategy in the future, prospective studies with clear definitions of radiological significance and progression are needed before it can be

adopted into routine clinical practice [31]. Until these are available, AS is limited by its reliance on repeat biopsies. Sooriakumaran et al. investigated the impact of multiple biopsies on outcomes of nerve-sparing robotic-assisted radical prostatectomy and found that men subject to multiple preoperative biopsies were more likely to become impotent postoperatively than those who had only received a single preoperative biopsy, hence arguing that a period of AS followed by RP resulted in worse functional outcomes than upfront RP [32]. Therefore, until mpMRI can reliably replace repeat biopsy, AS must not be considered to be a non-morbid management option.

Increasingly, there are alternative surgical procedures that are being offered to men with prostate cancer; these focal or tissue-preserving therapies are rationed on the basis that they offer a lower side-effect profile with equivalent cancer control [33–35]. Early results from a number of small studies have reported typically lower urinary incontinence and erectile dysfunction rates than contemporary RP series; however, it is important to note the data have limited external validity as patients are carefully selected, treated in very few expert centres, and the follow-up in these studies is very limited [34–36]. It also remains very difficult to assess outcomes of disease control in focally treated cases since surrogate measures such as PSA monitoring cannot be readily interpreted when the majority of the prostate gland is left behind [24]. The results of a non-randomised UK multi-centre study, called INDEX, using high-intensity focused ultrasound to randomise 140 men with a unilateral dominant lesion are awaited in 2016. Currently though, a note of caution should be sounded when considering focal ablation of the 'index' lesion in light of the publication of the recent Haffner et al. paper in *JCI* which discovered the lethal clone responsible for the metastases experienced by one PCa patient had arisen from a small, well-differentiated Gleason 3 lesion, rather than the prevalent Gleason 4 found elsewhere in his prostate [37]. The recently funded *P*artial *A*blation vs *R*adical prosta*T*ectomy (PART) trial will compare partial ablation of the prostate with RP in men with intermediate-risk unilateral prostate cancer and is a welcome addition to the field which otherwise consists of non-randomised studies. Until the results of these studies are available, focal therapy must be considered within the confines of research and cannot replace a tried-and-tested operation as the treatment of choice [38].

In summary, there have been some notable recent high-quality observational studies and an update of the SPCG-4 randomised controlled trial that show significant overall and disease-specific survival advantage for RP compared to RT or watchful waiting, respectively. Taken together, the evidence suggests that RP should be the first-choice treatment for young men, especially those with intermediate- and high-risk disease. Further research is needed to develop methods for distinguishing those men who may die from their disease and those men who can be reassured. Focal therapy is mechanistically interesting and may offer an option in men with low- and possibly even intermediate-risk disease; however, data is currently limited, and further studies are warranted before a change in clinical practice can be considered. The current evidence indicates that RP should be the gold standard treatment for the majority of men with clinically localised prostate cancer.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Daniel J. Stevens, Dr. Naomi L. Sharma and Dr. Roger Kirby each declare no potential conflicts of interest.

Dr. Ashutosh K. Tewari reports grants and personal fees from Intuitive Surgical Inc.

Dr. Prasanna Sooriakumaran reports grants from Intuitive Surgical Inc., personal fees from Novartis, personal fees from Spoonful of Sugar Ltd., grants from European Urology Scholarship Fund, outside the submitted work; and The Endourological Society, Intuitive Surgical Inc., Prostate UK, The Urology Foundation, and the European Urology Scholarship Fund for surgical training in radical prostatectomy.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.• Athene Lane J, Donovan JL, David M, et al. Active monitoring, radical prostatectomy, or radiotherapy for localised prostate cancer: study design and diagnostic and baseline results of the ProtecT randomised phase 3 trial. Lancet Oncol. 2014;15(10):1109–18. *Important baseline details and recruitment information for the soon to be published ProtecT RCT.*

2. Makarov DV, Trock BJ, Humphreys ED, et al. Updated nomogram to predict pathologic state of prostate cancer given prostate-specific antigen level, clinical stage, and biopsy Gleason score (Partin tables) based on cases from 2000 to 2005. Urology. 2007;69:1095–101.

3.•• Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med. 2014;370:932–42. *Updated results from the SPCG-4 trial.*

4.•• Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localised prostate cancer. N Engl J Med. 2012;367:203–13. *Results of the PIVOT trial.*

5. Roobol MJ, Bokhorst LP. The ProtecT trial: what can we expect? Lancet Oncol. 2014;15(10):1046–7.

6. Kates M, Tosoian J, Trock BJ et al. Indications for intervention during active surveillance of prostate cancer: a comparison of the Johns Hopkins and Prostate Cancer Research International Active Surveillance (PRIAS) protocols. BJUI. 2014; 12828

7. Surcel CI, Sooriakumaran P, Briganti A et al. Preferences for the management of high-risk prostate cancer among urologists in Europe: results of a web-based survey. BJUI Int. 2014; 12796

8.• 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(11):969–74. *Seminal paper comparing outcomes following treatment for prostate cancer.*
9. Zelefsky MJ, Eastham JA, Cronin AM, et al. Metastasis after radical prostatectomy or external beam radiotherapy for patients with clinically localized prostate cancer: a comparison of clinical cohorts adjusted for case mix. J Clin Oncol. 2010;28(9):1508–13.
10. Kupelian PA, Elshaikh M, Reddy CA, et al. Comparison of the efficacy of local therapies for localized prostate cancer in the prostate-specific antigen era: a large single-institution experience with radical prostatectomy and external-beam radiotherapy. J Clin Oncol. 2002;20(16):3376–85.
11. Grimm P, Billiet I, Bostwick D, et al. 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. BJUI. 2012;109(1):22–9.
12. Cooperberg MR, Vickers AJ, Broering JM, et al. Comparative risk-adjusted mortality outcomes after primary surgery, radiotherapy, or androgen-deprivation therapy for localized prostate cancer. Cancer. 2010;116(22):5226–34.
13. Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med. 2011;364:1708–17.
14.• Sun M, Sammon JD, Becker A, et al. Radical prostatectomy vs radiotherapy vs observation among older patients with clinically localized prostate cancer: a comparative effectiveness evaluation. BJUI. 2014;113:200–8. *High quality recently published observational study.*
15.• Hoffman RM, Koyama T, Kang-Hsien F, et al. Mortality after radical prostatectomy or external beam radiotherapy for localized prostate cancer. JNCI. 2013;105(10):711–8. *High quality recently published observational study.*
16. Daskivich TJ, Chamie K, Kwan L, et al. Improved prediction of long-term, other cause mortality in men with prostate cancer. J Urol. 2011;186(5):1868–73.
17.•• Sooriakumaran P, Nyberg T, Akre O, et al. Comparative effectiveness of radical prostatectomy and radiotherapy in prostate cancer: observational study of mortality outcomes. BMJ. 2014;348:1502. *Recently published observational study with near complete high quality dataset.*
18. Stattin P, Loeb S, et al. "To measure is to know. If you cannot measure it, you cannot improve it": statistical modeling cannot compensate for unmeasured bias. Eur Urol. 2014;65(4):701–3.
19. Rane A. Surgery or radiotherapy for prostate cancer? BMJ. 2014;348:g1580.
20. Matthew AG, Alibhai SM, Davidson T, et al. Health-related quality of life following radical prostatectomy: long term outcomes. Qual Life Res. 2014;23(8):2309–17.
21. Shroeck FL, Krupski T, Sun L, et al. Satisfaction and regret after open retropubic or robot-assisted laparoscopic radical prostatectomy. Eur Urol. 2008;54(4):785–93.
22. Nam RK, Cheung P, Herschorn S, et al. Incidence of complications other than urinary incontinence or erectile dysfunction after radical prostatectomy or radiotherapy for prostate cancer: a population-based cohort study. Lancet Oncol. 2014;15(2):223–31.
23. Schuessler WW, Schulmam PG, Clayman RV, et al. Laparoscopic radical prostatectomy: initial short-term experience. Urology. 1997;50(6):854–7.
24. Mayer EK, Winkler MH, Aggarwal R, et al. Robotic prostatectomy: the first UK experience. Int J Med Robot. 2006;2(4):321–8.
25. Novara G, Ficarra V, Mocellin S, et al. Systematic review and meta-analysis of studies reporting oncologic outcome after robot-assisted radical prostatectomy. Eur Urol. 2012;62(3):382–404.
26. Novara G, Ficarra V, Rosen R, et al. Systematic review and meta-analysis of perioperative outcomes and complications after robot-assisted radical prostatectomy. Eur Urol. 2012;62(3):431–52.
27. [http://www.baus.org.uk/Resources/BAUS/Documents/PDF%20Documents/Data%20and%20Audit/RadProsSnapshotPoster2012.pdf] Accessed 06/12/14.
28. Sooriakumaran P, Haendler L, Nyberg T, et al. Biochemical recurrence after robot-assisted radical prostatectomy in a european single-centre cohort with a minimum follow-up time of 5 years. Eur Urol. 2012;62(5):768–74.
29. Tosoian JJ, Trock BJ, Landis P, et al. Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. J Clin Oncol. 2011;29:2185–90.
30. Ganz PA, Barry JM, Burke W, et al. National Institutes of Health State-of-the-Science Conference: role of active surveillance in the management of men with localized prostate cancer. Ann Intern Med. 2012;156(8):591–5.
31. Shoots I, Petrides N, Giganti F, et al. Magnetic resonance imaging in active surveillance of prostate cancer: a systematic review. Eur Urol. 2014;10(050):S0302–2838.
32. Sooriakumaran P, Calway A, Sagalovich D, et al. The impact of multiple biopsies on outcomes of nerve-sparing robotic-assisted radical prostatectomy. Int J Impot Res. 2012;24(4):161–4.
33. Barret E, Ahallal Y, Sanchez-Salas R, et al. Morbidity of focal therapy in the treatment of localised prostate cancer. Eur Urol. 2013;63:618–22.
34. Ahmed HU, Freeman A, Kirkham A, et al. Focal therapy for localised prostate cancer: a phase I/II trial. J Urol. 2011;185:1246–54.
35. Ahmed HU, Hindley RG, Dickinson L, et al. Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study. Lancet Oncol. 2012;13:622–32.
36. Bahn D, de Castro Abeu AL, Gill IS, et al. Focal cryotherapy for clinically unilateral, low-intermediate risk prostate cancer in 73 men with a median follow-up of 3.7 years. Eur Urol. 2012;62:55–63.
37. Haffner M, Mosbruger T, Esopi DM, et al. Tracking the clonal origin of lethal prostate cancer. J Clin Invest. 2013;123(11):4918–22.
38. Dickinson L, Ahmed HU, Kirkham AP, et al. A multi-centre prospective development study evaluating focal therapy using high intensity focused ultrasound for localised prostate cancer: The INDEX study. Contemp Clin Trials. 2013;36(1):68–80.